Studies on Auranofin and Aurothioglucose in Rheumatoid Arthritis

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STUDIES ON AURANOFIN AND AUROTHIOGLUCOSE IN RHEUMATOID ARTHRITIS

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The studies presented in this thesis were performed in the out-patient's clinic of the Division of Rheumatology of the Department of Medicine (head: Prof. Dr. A. van 't Laar) Sint Radboud Hospital, Nijmegen, the Department of Rheumatology, Sint Maartenskliniek, Nijmegen and the Institute of Pharmacology (head: Prof. Dr. C.A.M. van Ginneken), Nijmegen, The Netherlands.

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Aan Marleen en Anneke

CONTENTS

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CHAPTER 1

INTRODUCTION

Rheumatoid arthritis is a systemic illness with usually polyarthritis as the most important manifestation (1). The aetiology of rheumatoid arthritis is unknown; a recent hypothesis is that, in a person with a distinct genetic make-up, some initiating agent not only leads to an immune response and inflammation but also to continued disease activity (2,3,4).

The natural history of rheumatoid arthritis is variable and capricious, ranging from episodes of polyarthritis alternated by spontaneous remissions to a rapidly progressive arthritis, sometimes with widespread systemic features (1). This stresses the need to evaluate therapeutic approaches on the basis of a controlled clinical study (5).

Many treatment modalities are involved in the management of rheumatoid arthritis, one of these being pharmacotherapy (6). The choice, which drug to be given at what time, is made depending on several factors: 1. how firm is the diagnosis?; 2. what is the extent and the intensity of the rheumatoid arthritis?; 3. is the patient's pain caused by arthritis or destructive lesions mainly?. The drugs used in the treatment of rheumatoid arthritis can be arranged under three headings.
Phase I drugs: non-steroidal anti-inflammatory drugs (NSAID): they give relief of pain and some reduction of the inflammation, with a rather prompt (hours or days) onset of therapeutic activity. They do not essentially influence the natural history of the disease (7,8).
Phase II drugs: remission-inducing drugs, also called slow-acting antirheumatic drugs or disease-modifying antirheumatic drugs: hydroxychloroquine, gold compounds and D-penicillamine. In contrast with phase I drugs one may not expect therapeutic effect of these drugs until after 8-12 weeks of treatment; apart from this later onset of action they possess the potency to induce a remission. However, the risks in terms of toxicity are much greater than those with phase I drugs (9,10).

Phase III drugs: immunoregulatory agents: azathioprine, cyclophosphamide, systemic corticosteroids and levamisole. They are generally more toxic than the phase II drugs (9,10). Phase I drugs are used in the treatment of rheumatoid arthritis, alone or in combination with phase II or III drugs. If the pain can be ascribed to destructive lesions, then treatment with simple analgesics (acetaminophen and glafenine) can be considered. Phase II drugs are generally reserved for patients who fail to respond to NSAID alone, with a proven diagnosis. Phase III drugs are given to patients refractory to the previously mentioned drugs.

Among the most widely and intensively studied drugs in the treatment of rheumatoid arthritis are the gold salts, aurothioglucose and aurothiomalate, which are intramuscularly administered (11). The exact mechanism by which gold compounds suppress chronic inflammation is still unknown. Since gold compounds were introduced in the treatment of rheumatoid arthritis in the beginning of this century because of their antimicrobial qualities, many other possible actions have been demonstrated (12,13). In the presence of gold compounds, lymphocytes do not respond appropriately (14), macrophages do not phagocytose efficiently (15), and multiple isolated enzyme systems are suppressed (16). Several controlled studies have shown that gold compounds are effective in the treatment of rheumatoid arthritis (17-22). For this reason they are still used in rheumatoid arthritis despite the high frequency of adverse reactions. The uncomfortable mode of administration has prompted a search for an orally absorbable gold compound which should be as effective as the intramuscularly administered gold compounds. Auranofin (S-triethylphosphine gold 2,3,4,6-tetra-O-acetyl-1-thio-B-D-glucopyranoside) is orally absorbed. Several preliminary studies, the first dating from 1976, have reported that this drug has antirheumatic activity (23). We started a formal clinical trial comparing the efficacy and safety of auranofin with aurothioglucose in October 1980. Patients had given informed consent for this study; the Hospi-

pital Ethics Committee had given approval to the protocol). To score therapeutic response we used a modification of an index of disease activity adapted from Mallya (24). The results of this single-blind study are presented in chapter 2 of this thesis. Some of the characteristics of auranofin and aurothioglucose are given in table I; the structural formulae of the two mentioned gold compounds are given in figure 1.

Table I. Characteristics of auranofin and aurothioglucose

	auranofin	ref	aurothioglucose
Physico-chemical properties			
lipid solubility	+	37	-
water solubility	-		+
monomeric	+	38	-
polymeric	-		+
Pharmacokinetic properties			
oral absorbation	20-30%		nihil
effective route	oral	39	intramuscular
peak serum level	1-2 h		6-8 h
serum protein binding	60-80%	36	60-100%
erythrocyte binding	20-40%	40	0-40%
serum t ½	17 days	39	6 days
route of elimination	fecal/renal		renal
dosing interval	12-24 h		1-4 weeks
Site of action	unknown		unknown
Clinical efficacy	probable		proven
classification of antirheumatic activity	probable phase II		phase II
Toxicity	gastrointestinal		dermal
	dermal		renal
			haematological
Legal status	experimental		marketed

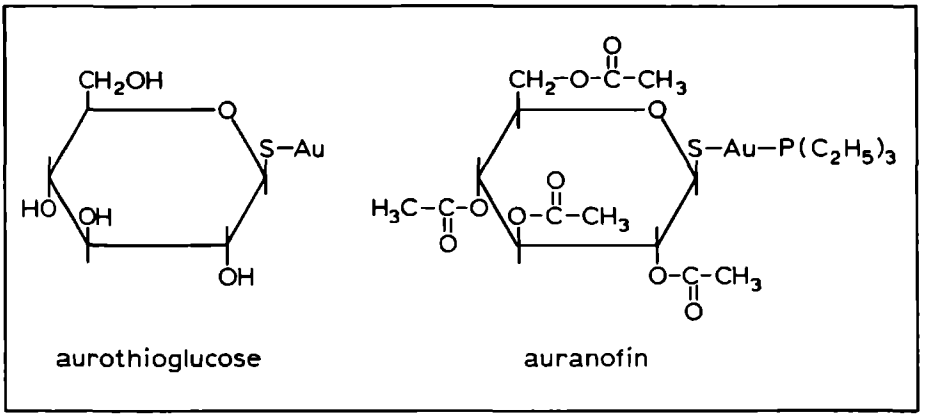

Figure 1. Structural formulae of aurothioglucose and auranofin.

As mentioned in the introductory remarks, some evidence suggests that the genetic make-up of a patient may influence the actual acquisition of rheumatoid arthritis (2,25,26). The patient's genetic disposition is probably also of importance for the extent and activity of the acquired disease: correlations were found between HLA-DR antigens and titre of rheumatoid factor (27), progress of rheumatoid arthritis and prognosis of disease (25). No association has so far been found between HLA antigens and the therapeutic response to drugs; some investigators found associations between HLA-DR antigens and toxic reactions to medication (25,26). In the context of the clinical trial described, we studied possible associations between HLA-antigens and therapeutic response to either auranofin or aurothioglucose, and also correlations between HLA-antigens and the development of toxic reactions to either auranofin or aurothioglucose (chapter 3).

It has been suggested that the toxic as well as the therapeutic mechanisms of gold action are immune-mediated (28,29,30). Several studies have shown a decline in immunoglobulin levels during chrysotherapy, and there are contradictory reports as to whether or not responders and non-responders show different declines in immunoglobulin levels (29,30). With regard to im-

munoglobulin levels no differences have so far been reported between toxic and non-toxic patients. At regular intervals we determined the immunoglobulin levels in our study population in order to detect differences between toxic and non-toxic patients. Results of these determinations are described in chapter 4 of this thesis. Drug-induced IgA deficiencies have been described for D-penicillamine and aurothiomalate (31,32). In chapter 5 we describe a patient who developed selective IgA deficiency during treatment with aurothioglucose. We have started attempts to identify the possible pathogenetic mechanism of this adverse reaction.

The toxicity profile of the orally absorbable gold compound is different from that of the intramuscularly administered gold compounds. A change in bowel habits is the most frequent adverse reaction to the orally absorbable gold compound. The clinical characteristics and the pathogenetic mechanism of this adverse reaction were unknown, and this prompted us to investigate them in our study population. We describe our findings in chapter 6 of this thesis.

Many attempts have been made to find correlations between the serum gold level and either efficacy or toxicity of gold compounds. Although most investigators agree that such an association does not exist (33), some keep claiming the contrary (34). Findings on serum gold levels in auranofin- and aurothioglucose-treated patients are presented in chapter 7 of this thesis.

In 1980 two articles were published about an association between the degree of gold binding to the erythrocytes and the occurrence of adverse reactions (35,36). These results were also contradictory. Since different methods of determining the amount of cell-bound gold were used, we compared these methods. Results are described in chapter 8.

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CHAPTER 2

A SINGLE BLIND COMPARATIVE STUDY OF AURANOFIN AND AUROTHIOGLUCOSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

Fifty-two patients with rheumatoid arthritis were studied in a trial comparing aurothioglucose and auranofin. Up to 40 patients have been followed up for more than one year. Twenty-six patients, 13 in each treatment group, dropped out during the first year of treatment. The main reason for discontinuing treatment with aurothioglucose was adverse reactions and, in the auranofin group, lack of efficacy.

In those patients who continued therapy the results of treatment were comparable; patients on aurothioglucose improved slightly more than auranofin-treated patients, the difference being statistically significant on only two occasions.

INTRODUCTION

The statement of Osler: "When the arthritic comes in the front door, the doctor wants to go out the back door", could be properly used to give expression to the restricted amount of drugs which are available in the second-line treatment of rheumatoid arthritis. This is also accentuated by the high percentage of serious adverse reactions occurring, often necessitating withdrawal of the drug. Gold is still the drug of choice in rheumatoid patients not responsive to NSAID and anti-malarials (1,2). The high percentage of adverse reactions caused by gold salts and the uncomfortable parenteral route of administration at weekly or longer intervals has led to the search for an orally absorbable and efficacious gold compound. Auranofin, an orally absorbable gold compound, developed by D.T. Walz et al., proved to be an effective anti-inflammatory and immunosuppressive agent in the adjuvant arthritic rat (3). In 1976, Finkelstein and Berglof demonstrated its effectiveness in patients with rheumatoid arthritis and it appeared to give rise to few adverse reactions (4,5). This drug may therefore afford interesting possibilities in the treatment of rheumatoid arthritis. The wide clinical spectrum of rheumatoid arthritis and its natural history with the occurrence of exacerbations and spontaneous remission, necessitate controlled studies for evaluating therapy. We compared the antirheumatic efficacy and safety of auranofin with the conventional intramuscularly administered gold compound aurothioglucose in a single, i.e. patient, blind controlled trial with one observer.

MATERIALS AND METHODS

Patients. Fifty-two patients with classical or definite rheumatoid arthritis according to the revised ARA criteria (6), participated in this study. Patients had an active disease defined as having at least three of the following features:
a. seven or more joints tender or painful on motion.
b. four or more swollen joints.

c. morning stiffness lasting for one hour or longer.
d. an erythrocyte sedimentation rate (Westergren) greater than 28 mm/h.
e. anaemia (Hb <8.7 mmol/l in males, <7.4 mmol/l in females).
Patients previously treated with corticosteroids, D-penicillamine, immunosuppressives or levamisole within 3 months or parenteral gold within 6 months of entry to the trial as well as patients with a history of gold toxicity or hypersensitivity to heavy metals, were excluded. Concomitant medication with NSAID, in a stable dose for one month prior to entry, was continued at the start of treatment; no other concomitant medication for rheumatoid arthritis was allowed. All patients gave their informed consent.

Drugs and dosing schedules. Patients on auranofin received 6 mg daily as a single morning dose with breakfast throughout the study. Patients on aurothioglucose (Auromyose; 20% oily suspension, Noury Pharma, Oss, The Netherlands) started with a test dose of 10 mg after which 50 mg weekly was given up to a cumulative dose of 1000 mg; thereafter the dose was reduced to 50 mg every 2-4 weeks. Placebo tablets containing lactose, and placebo injections containing 0.9% sterile saline were used as dummy drugs.

Trial design. The trial was a single-blind double-dummy study of auranofin versus aurothioglucose over 12 months. The patients entered the study during a period of a year, and they were allocated either to auranofin or aurothioglucose using a blocked randomization procedure. The patients were studied at the outpatient clinic; seven patients (three in the aurothioglucose group) were hospitalized during the first period of observation due to severe disease activity. Twenty-six patients were included in each of the two treatment groups. All patients were seen at each visit between 1.00 and 4.00 p.m. by the same observer (PvR). The following assessments were recorded fortnightly for the first two months and monthly thereafter:
a. duration of morning stiffness (h) on the day prior to the

visit.
b. time to onset of fatigue (h) on the day prior to the visit.
c. grip strength (kPa) using a Martin Vigorimeter.
d. pain assessment by analogue rating on a 10 cm line.
e. global assessment by analogue rating on a 10 cm line.
f. number of swollen joints.
g. number of joints with pain on palpation or passive movement.
h. physicians assessments of disease activity on a scale of 1 = none, 2 = mild local, 3 = mild general, 4 = moderate local, 5 = moderate general, 6 = severe local, 7 = severe general.

ARA anatomical stage and functional capacity according to Steinbrocker (7) were assessed three times during the study. Tests for rheumatoid factor were carried out 5 times during the study. Additional laboratory tests, undertaken at the same time as the clinical assessments, included haemoglobin, white blood cell count and differential, platelet count, ESR, creatinine, urea, uric acid, alkaline phosphatase, LDH, ALAT (SGPT), ASAT (SGOT) and bilirubin. The urine was examined microscopically and checked for protein. Blood samples for the assay of gold by atomic absorption spectrometry (8) were taken at the start of the trial and every two months thereafter. The blood samples were obtained just prior to the injection of aurothioglucose or its placebo.

Adverse reactions. Side-effects were recorded at each visit, reported either spontaneously by the patient or as replies to direct questions about: pruritus, skin rash, stomatitis and diarrhoea. Patients were withdrawn from the study if the platelet count fell below 100,000/mm^3, the white blood cell count was less than 3000/mm^3, the absolute polymorphonuclear count fell below 1500/mm^3, or proteinuria exceeded 500 mg/24 hrs. Patients with a severe generalized dermatitis or stomatitis were also withdrawn. Loose stools was defined as a relative increase in frequency of bowel movements and in fluidity of faeces as compared to the usual bowel habit of the same individual (9). The reported adverse reactions were tested using

an algorithm for assessing the probability of adverse drug reactions developed by Naranjo et al.(10). All adverse reactions in this report were classified as "probably" or "definitely" due to the administered drug. All patients who were withdrawn because of adverse reactions were followed until the reactions had cleared. Patients dropping out either because of lack of efficacy or side-effects were, if necessary, then treated with D-penicillamine.

Compliance. Returned drug count was used to measure patient compliance.

Assessment of response. We used a modification of a recently published activity index for rheumatoid arthritis by Mallya et al. (11). By using the factor analytic methods, Varimax and Quartimax, two sets of five variables were found to measure the factor "disease activity" most reliably. Providing equal weighting for both sets, we did not include pain scale and grip strength results in our index, in contrast with Mallya et al. The four components used in our index were: duration of morning stiffness, total number of tender joints, haemoglobin and erythrocyte sedimentation rate (ESR). The gradings for these are shown in table I. Dividing the total of all grades by four gave a mean value which we used as an index of disease activity (IDA). The results are expressed as

Table I. Grading of clinical findings.

Grade	morning stiffness (min)	number of tender joints	Hb(mmol/l) ♂	Hb(mmol/l) ♀	ESR(mm/h)
1	<10	≤2	≥8.7	≥7.4	0-20
2	10-30	3-7	8.1-8.6	6.9-7.3	21-45
3	31-120	8-17	6.2-8.0	5.3-6.8	46-80
4	>120	≥18	≤6.1	≤5.2	≥81

Table II. IDA correlated with each of its components.

		ESR	Hb	MS	No. of tender joints
IDA	r	0.59	0.53	0.41	0.45
	range	0.51-0.70	0.32-0.64	0.15-0.52	0.27-0.63

the percentage improvement from baseline (PIDA) in order to correct for initial differences between the two treatment groups. As shown in table II each of the four components of the IDA were equally weighed in the index.

Statistical analysis. The t-test for independent groups with the pooled variance formula was used for assessment of statistical significance of differences between the treatments. P values of <0.05 were considered to be statistically significant. Pearson's correlation coefficient was used to correlate the results of morning stiffness, number of tender joints, ESR and haemoglobin with the index of disease activity.

RESULTS

Fifty-two patients equally divided between the two treatment groups entered the study. The groups were comparable for most of the initial clinical and laboratory assessments, the only differences being that patients in the aurothioglucose group had a longer disease duration and had been more commonly treated in the past with hydroxychloroquine compared with the patients in the auranofin group (table III). Until now 40 patients have been followed up for at least one year. Twenty-six patients (50%) were withdrawn during the course of the study. Thirteen patients were withdrawn for adverse reactions, 11 of whom were in the aurothioglucose group. Eleven patients were withdrawn due to lack of efficacy, 10 of whom were in the auranofin group. One patient in each treatment group was withdrawn for reasons unrelated to the treatment.

Table III. Clinical characteristics of the patients.

	auranofin	aurothioglucose
Total number of patients	26	26
Sex distribution		
female	17	21
male	9	5
Age distribution (yr)		
mean	49	56
SD	13	9
range	27-69	41-69
Seropositive	22	22
ESR (mm/h)		
mean	58	51
SD	36	33
range	15-147	8-140
Hb (mmol/l)		
mean	7.6	7.6
SD	1.0	0.9
range	5.6-9.3	5.5-10.3
Disease duration (yr)		
mean	2.5	5.1
SD	3.1	6.9
range	0.3-11.8	0.3-33.3
Previous therapy		
gold	1	2
hydroxychloroquine	8	20
ARA anatomical class		
I	8	4
II	15	19
III	3	3
mean	1.8	2.0
Steinbrocker functional class		
I	0	1
II	16	16
III	10	9
mean	2.4	2.3
Index of disease activity		
mean	2.5	2.4
SD	0.5	0.5
range	1.5-3.8	1.5-3.9
HLA haplotype		
DR-4	17	16
DR-3	3	6

Figure 1.

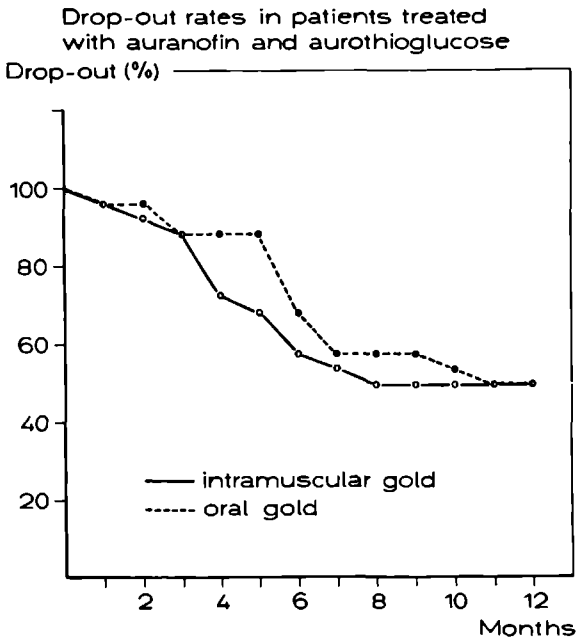

Figure 2.

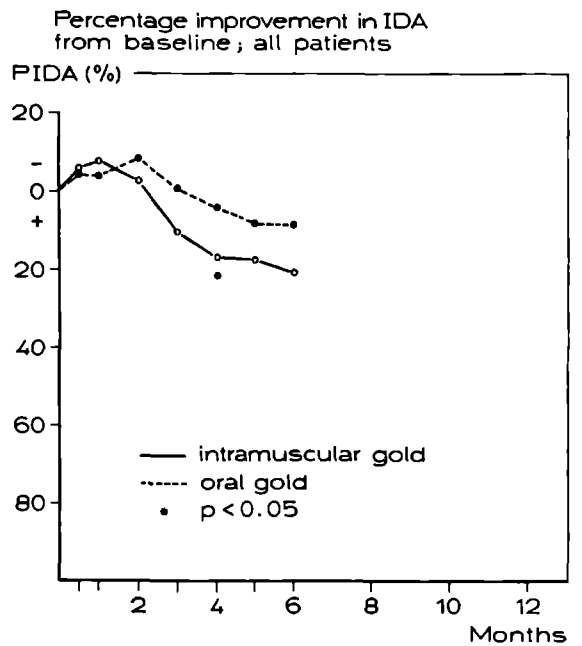

Figure 3.

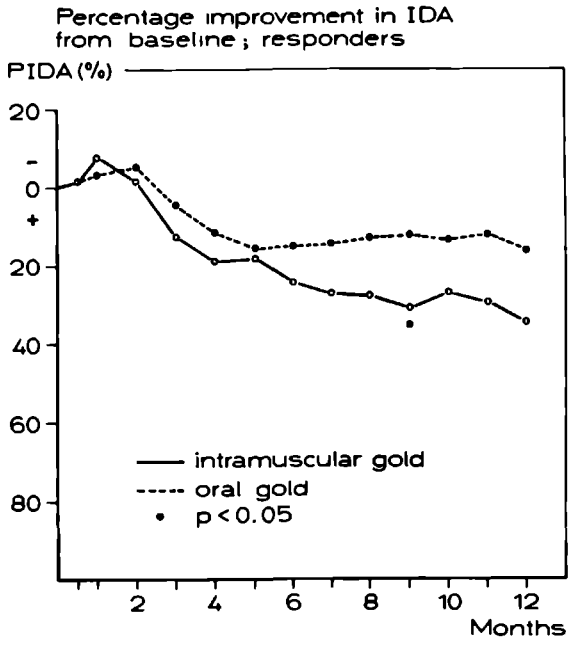

Figure 4.

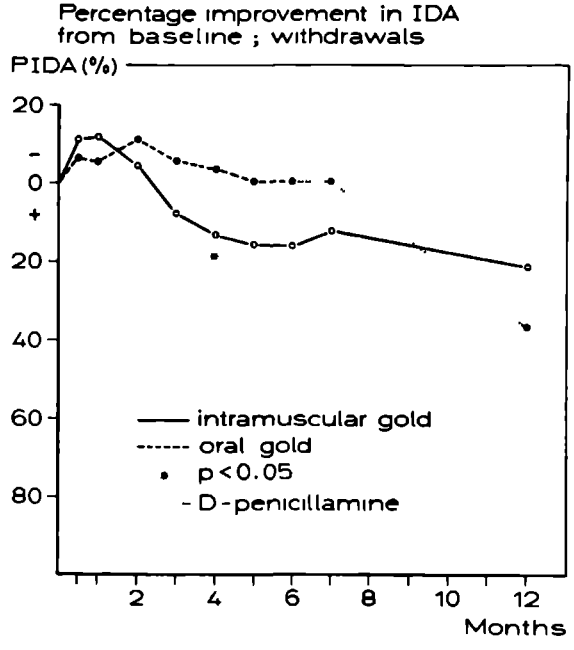

Table IV. List of adverse reactions and withdrawals.

	Aurothioglucose		Auranofin	
	no. of patients	no. of withdrawals	no. of patients	no. of withdrawals
Adverse drug reaction				
dermatitis	15	8	3	1
loose stools	1	0	11	1
stomatitis	2	1	0	0
proteinuria	1	1	0	0
polyneuropathy	1	1	0	0
IgA deficiency	1	0	0	0
Total adverse reactions	21	11	14	2
Lack of efficacy	1	1	10	10
Not drug related				
intercurrent illness	1	1	0	0
lack of cooperation	0	0	1	1
TOTAL	23	13	25	13

Some patients experienced more than one adverse reaction at the same time.

The average compliance to prescription was 98.5% (expressed as the average number of tablets taken per month divided by average number of tablets described per month times 100%).

The commonest side-effect in the auranofin patients was loose stools; 11 patients experienced this side-effect during some period of the trial, but only in 1 patient was it the reason for withdrawal. Three patients in the auranofin group had dermatitis, in one case being a generalized dermatitis unresponsive to dose decrement. After withdrawal the dermatitis disappeared within two weeks. Rechallenge with auranofin caused a recurrence of the dermatitis. The commonest side-effect in the aurothioglucose patients was dermatitis, 8 patients being withdrawn for this reason. The dermatitis persisted for several months after withdrawal of treatment. Reasons for drop-out and the drop-out rates for both treatment groups are shown in table IV and figure 1 respectively.

Table V. Changes in rheumatoid factor for both treatment groups

change in tube dilution	auranofin	aurothioglucose
change of less than 2	17*	19
decrease of ≥2	5	7
increase of ≥2	4	1

* number of patients

For evaluating therapeutic response we compared the percentual changes in IDA from baseline (PIDA) for all patients in both treatment groups up to the 6th month of treatment. Improvement was seen for both therapies; at month 4, the aurothioglucose treated patients were significantly more improved than the auranofin treated patients ($p < 0.05$), as shown in figure 2. We also compared patients in both treatment groups who completed one year treatment. Again, improvement was seen in patients in both treatment groups, with significantly more improvement for aurothioglucose treated patients at month 9 ($p < 0.05$), as shown in figure 3. Patients withdrawn in the auranofin treated group did not show any improvement since that was mainly the reason for drop-out. When switched to D-penicillamine a rapid onset of response was seen, leading to an improvement in IDA of about 35% at month 12. The drop-outs in the aurothioglucose group, mainly withdrawn because of side-effects, improved up to month 12 without other therapy (figure 4).
Changes in rheumatoid factor for both treatment groups are given in table V. Three patients in the aurothioglucose group and none in the auranofin group became seronegative. Sixteen patients in the aurothioglucose group and 13 patients in the auranofin group were able to reduce the dose of concomitantly administered NSAID.

DISCUSSION

Previous studies have demonstrated the superiority of auranofin, in a dose of 6 mg daily, to placebo in the treatment of

rheumatoid arthritis (12,13). In the present study we compared the efficacy and safety of aurothioglucose and auranofin. High numbers of withdrawals from both treatments forced us to subdivide the two treatment groups into three populations. The number of withdrawals was equal in both treatment groups. The reason for withdrawal was mainly lack of efficacy in the auranofin patients and side-effects in the aurothioglucose patients. Loose stools was the most frequent adverse reaction in the auranofin group, but led to withdrawal of only one patient. The commonest side-effect in the aurothioglucose patients was dermatitis leading to 8 withdrawals. When the two treatment groups as a whole were compared up to the 6th month of therapy, the aurothioglucose patients improved slightly more than the auranofin patients, reaching a statistically significant level only at month 4. The same was seen when all patients treated up to 12 months (responders) were compared, a statistically significant difference being found only at month 9. Comparison of the withdrawn patients showed, as expected, no improvement in the auranofin patients; the aurothioglucose patients improved with a statistically significant difference at month 4. This improvement was sustained until month 12. Auranofin patients withdrawn because of lack of efficacy were next treated with D-penicillamine; after 6 months they had improved to the same extent as the aurothioglucose treated patients after one year of treatment. The mean onset of response was slightly earlier in the aurothioglucose patients than in the auranofin patients (month 3 versus month 4).
As to the difference in disease duration in the two treatment groups, no statistically significant correlations were found between the IDA and the duration of disease, so this could not explain the difference in response.

In conclusion, we would say that concerning safety, auranofin had far less serious side-effects and if present they cleared faster than those associated with aurothioglucose. However, concerning efficacy, aurothioglucose was more effective than auranofin, although the difference only occasionally reached

statistical significance. Whether increasing the dose of auranofin in the non-responders will improve the efficacy remains a subject for further study.

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CHAPTER 3

ASSOCIATION OF HLA ANTIGENS, TOXIC REACTIONS AND THERAPEUTIC RESPONSE TO AURANOFIN AND AUROTHIOGLUCOSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

To investigate the possible relation between HLA antigens and either favourable clinical response or toxic reaction to two different gold compounds: aurothioglucose and auranofin (a new orally absorbable gold compound), we studied 50 patients with rheumatoid arthritis prospectively. Of the 25 aurothioglucose-treated patients response to treatment could not be evaluated in four patients because of early toxicity. Nine patients showed an excellent response, while 12 were moderate or non-responders. Four of the 9 excellent responders were HLA-DR3 positive, but none of the 12 moderate or non-responders possessed this antigen ($p < 0.025$). In accordance with previous reports HLA-DR3 was found more frequently in patients developing toxicity on aurothioglucose than in those who did not (RR = 5.6). No association was found between HLA antigens and favourable clinical response in 25 auranofin-treated patients. Two of them showed a severe adverse reaction, neither of them being DR3-positive. HLA-DR3 positivity is associated not only with drug toxicity, but also with excellent responderships to aurothioglucose treatment.

INTRODUCTION

Genetic factors play a role in the pathogenesis of rheumatoid arthritis (RA), since HLA-DW4/DR4 has been shown to be significantly increased in patients with the latter disease (1). Recently studies have been reported on associations between HLA antigens and the occurrence of side effects on slow acting antirheumatic drugs. HLA-DR3 was found to be increased in RA patients with gold- and/or D-penicillamine-induced proteinuria (2), dermatitis (3,4) and haematological abnormalities (5). In addition, HLA-B27 was shown to occur more frequently in RA patients with levamisole-induced agranulocytosis (6,7). Interestingly, no detailed studies have so far been published on a possible association between HLA antigens and responsiveness to drug treatment in RA, although one congress presentation reports on the absence of such an association (8). It is conceivable that like studies may have been hampered by difficulties in quantitating clinical response to drug treatment in RA patients. In the present study we made an attempt to overcome this problem by using a modification of a recently developed scoring system (9) for the evaluation of disease activity in RA. Using this system we evaluated clinical responses to aurothioglucose or auranofin, a new orally absorbable gold compound, in the context of a patient blind study comparing the efficacy and safety of these drugs. We studied the possible associations between HLA antigens and clinical response and/or toxicity in these patients.

PATIENTS AND METHODS

Patients. In this study, an intramuscularly administered gold compound (aurothioglucose) and an orally absorbable gold compound (auranofin) were compared for efficacy. Fifty caucasian patients with classical or definite rheumatoid arthritis (RA) according to the revised ARA criteria (10), participated the study. The patients had active disease, defined as showing at least three of the following features: a) seven or more

tender joints or joints painful on motion; b) four or more swollen joints; c) morning stiffness lasting one hour or longer; d) an erythrocyte sedimentation rate (Westergren) exceeding 28 mm/h; e) anaemia (Hb <8.7 mmol/l in males, <7.4 mmol/l in females). Twenty-one of the 25 patients of the aurothioglucose group were analysed for a correlation between HLA-DR phenotype and response to therapy. In four patients, treatment had to be stopped within 4 months in view of adverse reactions. Two of the 25 patients of the auranofin group could not be analysed for response evaluation; one was withdrawn within two months of treatment in view of an adverse reaction, the other dropped out due to non-compliance after two months of treatment.

Drugs and dosage schedule. Patients on auranofin received 6 mg daily as a single morning dose. After a test dose of 10 mg, patients on aurothioglucose received 50 mg weekly up to the 20th week, after which the dose was reduced to 50 mg every 2-4 weeks.

Evaluation of response. Clinical and laboratory assessments were made before institution of treatment, biweekly during the first two months and monthly thereafter. This schedule was also maintained if patients were withdrawn because of toxicity, until institution of another form of therapy. A modification of a recently published activity index for rheumatoid arthritis (9) was used for evaluation of response. The four components of our index of disease activity (IDA) and its gradings are shown in table I. The degree of improvement on therapy in each patient was obtained by determining the percentage of improvement from baseline (PIDA). The mean IDA and the mean PIDA were calculated for each patient from the assessments of the 4th through the 12th month of treatment. Patients withdrawn from the study in view of toxicity were included for response evaluation if they had been treated with the gold compound for at least 4 months.

Table I. Grading of clinical findings for definition of IDA.

Grade	Duration of morning stiffness (min)	Number of tender joints	Hb(mmol/l) ♂	Hb(mmol/l) ♀	ESR(mm/h)
1	<10	≤2	≥8.7	≥7.4	0-20
2	10-30	3-7	8.1-8.6	6.9-7.3	21-45
3	31-120	8-17	6.2-8.0	5.3-6.8	46-80
4	>120	≥18	≤6.1	≤5.2	≥81

Criteria of response. Evaluation of response was based on the degree of improvement in IDA from baseline (PIDA) as well as on the degree of disease activity (IDA) attained. The mean IDA as well as the mean PIDA were arbitrarily divided into six classes (table II).

Table II. Grading of the mean index of disease activity (IDA) and of the mean percentage of improvement in IDA from baseline (PIDA).

Class	IDA	PIDA (%)
1	1-1.5	51-60
2	1.6-2.0	41-50
3	2.1-2.5	31-40
4	2.6-3.0	21-30
5	3.1-3.5	11-20
6	3.6-4.0	≤10

Patients were considered to have shown an excellent response if their mean IDA and PIDA, measured over a 8-month period, both were in the first three classes. Patients withdrawn due to toxicity were considered to have shown an excellent response if their mean IDA and mean PIDA, measured over a period of at least 3 months, were in the first three classes. Non-

responders were patients who either improved less than 10% from baseline or deteriorated (class 6 PIDA). Moderate responders were patients not covered by the previous classifications.

Assessments of adverse reactions. Patients were considered to have developed adverse reactions to aurothioglucose or auranofin if any of the following signs were observed: severe pruritus, rash or stomatitis which diminished after stopping treatment; proteinuria exceeding 500 mg/24 h for more than two weeks; a fall in platelet count below 100,000/mm^3; white blood cell count less than 3000/mm^3 or an absolute polymorphonuclear count below 1500/mm^3. Twenty-five patients in the aurothioglucose group and 24 patients in the auranofin group could be analysed for adverse reactions.

HLA typing. HLA typing was done after a 6-month trial period. The results of typing were not known to the observer (PvR) until the response classification had been made. For HLA-ABC typing, standard NIH-procedures were used. HLA-DR typing was done on B cells after enrichment by AET rosetting, using 58 sera that defined DR1-DRW10 as well as MB and MT specificities. A control group consisted of 277 healthy voluntary blood donors living in the same region as the patients.

Statistical analysis. Fisher's exact test for comparison of two proportions was used to assess statistical significance of data.

RESULTS

Comparison of the two treatment groups. The aurothioglucose-treated and the auranofin-treated patients were comparable as to age and sex distribution, seropositivity, disease activity and duration of disease. HLA-ABC antigens had a normal frequency distribution in both patient groups. Compared with the normal population, HLA-DR4 frequency was found to be increased in both aurothioglucose- and auranofin-treated patients (56% and 68% respectively).

Table III. HLA-DR3 frequency and response to aurothioglucose and auranofin.

Response	AUROTHIOGLUCOSE			AURANOFIN		
	DR3 +	DR3 -	total	DR3 +	DR3 -	total
excellent	4 *	5	9	1	4	5
moderate/no response	0	12	12	2	16	18

* $p < 0.025$ Fisher's exact test

No statistically significant differences were found between the aurothioglucose-treated patients, the auranofin-treated patients and a group of healthy controls with respect to the distribution of the other HLA-DR antigens.

HLA and response. Twenty-one patients in the aurothioglucose group were analysed for a correlation between clinical characteristics, HLA antigens and response after at least 4 months of treatment. Nine patients responded excellently (mean IDA and PIDA both in the first three classes, table II) to treatment according to our scoring criteria. Seven patients were moderate responders and 5 were non-responders. Excellent, moderate and non-responders were equal in clinical characteristics and distribution of HLA-ABC antigens. Four of the 9 excellent responders were HLA-DR3-positive, whereas none of the 12 moderate or non-responders was positive for HLA-DR3 ($p < 0.025$, table III). Response to treatment with auranofin was reviewed in 23 patients. Only five patients showed an excellent response; 7 were moderate and 11 were non-responders. Three patients evenly distributed over these 3 groups, were HLA-DR3-positive (table III).

HLA and adverse reaction. Four patients had such severe adverse reactions that treatment with aurothioglucose had to be stopped within 4 months (3 dermatitis, 1 polyneuropathy); two of them were HLA-DR3-positive. Ten additional patients were

Table IV. HLA-DR3 frequency and toxic reaction to aurothioglucose.

	DR3 +	DR3 -	total
Toxic patients			
- withdrawn <4 months	2	2	4
- withdrawn ≥4 months	3	7	10
Non-toxic patients	1	10	11

withdrawn between 4 and 12 months of treatment in view of severe adverse reactions to aurothioglucose (8 dermatitis, 1 stomatitis, 1 proteinuria). Three of them were HLA-DR3-positive. In the non-toxic group of 11 patients, only one was DR3-positive. The differences between the three groups did not attain statistical significance (table IV). At institution of treatment the toxic and the non-toxic patients were comparable as to age and sex distribution, seropositivity, disease duration, activity of disease and distribution of HLA-ABC antigens. Only two patients in the auranofin group showed a severe adverse reaction, which made it necessary to stop treatment. Neither of them was HLA-DR3-positive.

DISCUSSION

Our data indicate an association between HLA-DR3 positivity and excellent clinical response in the aurothioglucose treated patients with RA. This association could not be shown in the auranofin treated group, probably because of smaller numbers of DR3 positive patients and of excellent responders. Both patient groups were comparable in the frequency of HLA antigens and showed an increased HLA-DR4 frequency as compared to healthy controls, in accordance with previous reports (1,3,11). To our knowledge only one group has studied possible associations between HLA antigens and clinical response to slow acting antirheumatic drugs, in this case aurothiomalate (8). These

authors were unable to find any association, but excluded patients with drug-induced toxicity. We consider it justifiable to include in the analysis those patients withdrawn from the study because of adverse reactions, who had been treated for at least four months, since after that time clinical improvement can be attributed to gold therapy. The importance of this is illustrated by the fact that four of the patients in the aurothioglucose excellent responder group were withdrawn because of adverse reactions, occurring after at least four months of treatment, two of them being HLA-DR3 positive.

Several recent studies have shown associations between HLA-DR3 and gold- and/or D-penicillamine-induced toxicity, including proteinuria (2), skin rashes (3,4) and haematological abnormalities (5). In our study 5 of the 6 DR3 positive patients in the aurothioglucose treated group, developed toxic reactions, mainly skin rashes, suggesting an association. However, numbers were too small to reach statistical significance. Another interesting observation is that two out of four patients with early aurothioglucose-induced toxicity (occurring in the first 4 months) were DR-3-positive, whereas only three out of ten late toxicities (after 4 months) were positive for this antigen, suggesting that DR3-positive patients are prone to early toxicity. Similar observations have been done in aurothioglucose- or D-penicillamine-induced proteinuria, showing that early and heavy proteinuria was more frequent in DR3-positive than in DR3-negative patients (12).

The present data indicate that DR3 positive patients with RA may not only be prone to gold-induced toxicity, as has been reported earlier (2,3,4), but also to favourable clinical response. Our data do not allow conclusions as to whether in the DR3-positive group proneness to develop drug toxicity is associated with excellent respondership. If this were true, it would be worthwhile to treat this group of patients with lower doses of gold in an attempt to avoid toxicity and at the same time retain excellent respondership.

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CHAPTER 4

SERUM IgA AND GOLD-INDUCED TOXICITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Serum immunoglobulin concentrations were measured in 25 patients with rheumatoid arthritis at month 0,1,3,6 and 12 of aurothioglucose treatment. Significant lowering of IgA and IgM levels was found at month 3 and thereafter, and of IgG at month 12 only. When patients who developed drug-induced toxicity at any time during treatment (toxic group) were compared with those who did not (non-toxic group), serum levels of IgA and to a lesser degree of IgG, but not of IgM, were found to be significantly lower in the toxic than in the non-toxic group, both at the onset and during treatment, except for IgG at month 12. In addition the decline of serum IgA, but not of IgG and IgM, during treatment was greater in the toxic than in the non-toxic group. When measured at the moment of toxicity, only IgA but not IgG and IgM, was significantly lower than in sera of patients not toxic at that moment. During treatment 6 patients developed serum IgA levels below normal; they all had or developed severe drug toxicity. The serum IgA concentration in patients with rheumatoid arthritis seems to be related to whether or not aurothioglucose-induced toxicity occurs.

INTRODUCTION

Since more than 50 years gold salts have been successfully used in the treatment of rheumatoid arthritis. Their main disadvantage is the frequent occurrence of side effects, which often necessitate discontinuation of treatment (1). Mechanisms involved in the development of drug toxicity are largely unknown, although genetic factors have recently been implicated for gold-induced proteinuria (2), skin rashes (3,4) and thrombocytopenia (5). Several observations indicate a role of immune mechanisms in the development of gold-induced toxicity. Gold-induced proteinuria was shown to be associated with immune complex glomerulonephritis (6) and drug toxicity is often preceded by or associated with peripheral blood eosinophilia (7), suggesting a type I hypersensitivity reaction. In addition it has been suggested that gold-induced dermatitis is mediated by type IV hypersensitivity reactions (8).
We report on a prospective study of serum immunoglobulin G, A and M in patients with rheumatoid arthritis with and without toxic reactions to aurothioglucose during treatment with this drug. This study was performed in connection with a clinical trial comparing the efficacy and toxicity of aurothioglucose and auranofin, a new orally absorbable gold compound (9). Since patients treated with auranofin developed toxicities on only a few occasions, data on these patients were not suitable for the purpose of this study and were therefore excluded. Our data suggest that the level of serum IgA in patients with rheumatoid arthritis is related to whether or not aurothioglucose-induced toxicity occurs, toxicity occurring predominantly in patients with normal or subnormal IgA levels.

PATIENTS AND METHODS

Patients. Twenty-five patients with definite or classical rheumatoid arthritis according to the revised American Rheumatism Association criteria (10) were treated with aurothioglucose in a prospective clinical study. All patients had ac-

Table I. Clinical characteristics of all patients and of the toxic and non-toxic group at the start of treatment.

	all patients n = 25	toxic group n = 14	non-toxic group n = 11
Sex distribution			
female	20	12	8
male	5	2	3
Age distribution (yrs)			
range	39-69	39-68	47-69
mean ± SD	56±9	55±10	55±7
Seropositive	21	11	10
ESR (mm/h)			
range	8-140	8-110	12-140
mean ± SD	50±33	43±27	59±40
Hb (mmol/l)			
range	5.5-10.3	5.5-10.3	5.9-8.4
mean ± SD	7.6±1.0	7.6±1.2	7.5±0.7
Disease duration (yrs)			
range	0.3±33.3	0.3±33.3	0.8±14
mean ± SD	5.1±6.8	4.0±8.5	5.6±4.3
Serum gold (µg/100 ml)			
range	145-460	145-348	158-460
mean ± SD	259±79	279±38	241±104
HLA antigen			
DR3	6	5	1
DR4	15	9	6

tive disease unresponsive to non-steroidal anti-inflammatory drugs (NSAID) and antimalarial agents. Clinical characteristics of the patients are given in table I. Systemic corticosteroids, D-penicillamine, immunosuppressive drugs or levamisole had not been administered within 3 months prior to inclusion in the study.

Drug regimen. After a test dose of 10 mg, 50 mg aurothioglu-

cose weekly was given intramuscularly during 20 weeks. The dose was then reduced to 50 mg every 2 weeks, up to a cumulative dose of 1500 mg; thereafter 50 mg was given every three weeks to the end of the study. Only concomitant medication with NSAID was allowed during the study. Adverse reactions were searched for at each aurothioglucose injection, and included any of the following signs or symptoms, if reversible after stopping aurothioglucose treatment: severe pruritus, rash or stomatitis, proteinuria exceeding 500 mg/24 h for more than two weeks; a fall in platelet count below 100,000/mm^3, white blood cell count below 3000/mm^3, or an absolute polymorphonuclear count below 1500/mm^3. Thirteen patients were withdrawn during the first year of treatment in view of generalized dermatitis (one patient had proteinuria at the same time), and one in view of polyneuropathy. These 14 patients made up the toxic group. Eleven patients without or with minimal local dermatitis not necessitating discontinuation of treatment in the course of one year formed the non-toxic group.
No differences in clinical characteristics were found between the toxic and the non-toxic group; in accordance with the literature (3) the HLA-DR3 frequency was increased in the toxic group as compared with the non-toxic group (table I).

Immunoglobulin assay. Immunoglobulin levels were determined at the start of the trial and 1,3,6 and 12 months thereafter by the radial immunodiffusion method of Mancini (11) using standard commercially obtained immunodiffusion plates and standards (Behring Werke, Marburg, W-Germany). Normal serum immunoglobulin concentrations are (mean $\pm$ SD): IgA 2.0 $\pm$ 0.6 g/l (119 $\pm$ 36 I.U./ml), Igm 1.1 $\pm$ 0.4 g/l (127 $\pm$ 46 I.U./ml) and IgG 12.5 $\pm$ 2.1 g/l (144 $\pm$ 24 I.U./ml).

Statistical analysis. A paired variate t-test was used to determine the statistical significance of the changes in immunoglobulin levels before and during gold treatment. Student's t-test for independent groups was used to assess the statistical significance of differences between toxic and non-toxic

patients.

RESULTS

Serum immunoglobulin levels in the total group of patients before and during treatment with aurothioglucose are shown in table II. Differences between baseline and serial values were analysed by a paired variate t-test. Statistically significant differences were found for IgA and IgM levels at month 3 and thereafter and for IgG at month 12. Comparison of the immunoglobulin levels of the toxic and the non-toxic group revealed statistically significantly lower serum levels of IgA and to a lesser degree of IgG both at the onset and during treatment, except for IgG at month 12 (table II). However, no significant differences in IgM level were seen. For IgG the decline in the toxic group was comparable with that in the non-toxic group. For IgA, however, the decline was significantly greater in the toxic than in the non-toxic group ($p < 0.02$, at month 6). We also compared the serum immunoglobulin levels at month 6 and 12 in patients with an adverse reaction at that time with those in patients without an adverse reaction. Significantly lower IgA levels were found in the patients with an adverse reaction, while no statistically significant differences were found in IgG and IgM levels (table III). Six patients, all belonging to the toxic group, developed IgA levels below the normal range during treatment. The adverse reaction appeared at the same time as or after the serum IgA level became subnormal. Three toxic patients with subnormal serum IgA levels had subnormal IgM levels at the same time. None of the other patients developed subnormal IgM levels during treatment, and subnormal IgG levels were never found.

DISCUSSION

Adverse reactions remain the major limiting factor of gold therapy for rheumatoid arthritis. The present data indicate that serum IgA levels in these patients are somehow related

Table II. Serum immunoglobulin levels in the total group of aurothioglucose-treated patients and in the toxic and non-toxic group

month	IgA● total group○	IgA toxic group	IgA p* value	IgA non-toxic group	IgG total group	IgG toxic group	IgG p* value	IgG non-toxic group	IgM total group	IgM toxic group	IgM p* value	IgM non-toxic group
0	3.32±1.18 (25)	2.97±1.16 (14)	<0.02	4.62±1.88 (11)	17.59±5.49 (25)	15.88±4.82 (14)	<0.05	21.67±6.83 (11)	1.34±0.58 (25)	1.41±0.55 (14)	>0.05	1.52±0.69 (11)
1	3.26±1.13 (25)	2.77±0.97 (14)	<0.01	4.70±1.89 (11)	17.89±7.41 (25)	15.45±6.54 (14)	<0.01	22.81±5.21 (11)	1.39±0.59 (25)	1.47±0.68 (14)	>0.5	1.35±0.46 (11)
3	2.74±1.33+ (24)	2.14±1.35 (13)	<0.01	4.20±1.90 (11)	17.73±5.47 (24)	15.39±4.75 (13)	<0.01	21.21±5.21 (11)	1.14±0.55+ (24)	1.02±0.54 (13)	>0.1	1.33±0.52 (11)
6	2.66±1.24++ (20)	1.54±1.13 (10)	<0.01	4.05±1.89 (10)	16.73±4.65 (20)	14.73±5.01 (10)	<0.05	19.66±4.07 (10)	1.17±0.51+ (20)	0.96±0.52 (10)	>0.1	1.25±0.41 (10)
12	2.40±1.28+++ (12)	1.07±0.39 (4)	<0.01	3.50±1.62 (8)	14.17±3.37+ (12)	11.46±3.87 (4)	>0.05	15.97±2.26 (8)	1.09±0.41+++ (12)	1.00±0.29 (4)	>0.5	1.13±0.47 (8)

● Serum immunoglobulin at month 1,3,6 and 12 was compared with that of month 0 by a paired variate t-test; + = $p < 0.05$; ++ = $p < 0.01$; +++ = $p < 0.001$.

○ Mean ± SD; numbers in parentheses indicate number of patients.

* Student's t-test for independent groups, i.e. the toxic and non-toxic group.

Table III. Serum immunoglubulin concentrations at month 6 and 12 of treatment in patients with and without an adverse reaction at that moment.

	IgA+			IgG			IgM		
month	adverse reaction *present*	p* value	adverse reaction *absent*	adverse reaction *present*	p* value	adverse reaction *absent*	adverse reaction *present*	p* value	adverse reaction *absent*
6	1.67±0.93 (4)	<0.05	3.28±2.00 (16)	15.67±5.20 (4)	>0.5	17.89±5.20 (16)	1.11±0.74 (4)	>0.5	1.15±0.41 (16)
12	1.07±0.39 (4)	<0.01	3.50±1.62 (8)	11.46±3.87 (4)	>0.05	15.97±2.26 (8)	1.00±0.29 (4)	>0.5	1.13±0.47 (8)

+ Mean ± SD; numbers in parentheses indicate number of patients.

* Student's t-test for independent groups.

to whether or not drug toxicity occurs. Comparison of patients who developed toxicity at any time during aurothioglucose treatment (toxic group) with those who did not (non-toxic group) indicated a lower level of IgA in the former group at all measurements. In addition, the decline in IgA during treatment was greater in the toxic than in the non-toxic group. Of special interest was the observation that all patients who developed subnormal IgA levels during treatment were or became toxic later on.

The relationship between (relatively) low IgA levels and gold toxicity is obscure. The number of IgA measurements in our study is too small to warrant firm conclusions about a precise time relationship between a decline in serum IgA and the development of toxicity. However, of the 6 patients with definitely subnormal IgA levels, 3 already had low IgA levels before toxicity developed, whereas the reverse was not observed in this study. This fact, together with the observation that the toxic group showed lower IgA levels from the start, i.e. before toxicity developed, suggests that a decline in serum IgA at least may facilitate adverse reactions rather than being an expression of drug toxicity itself. If this statement is correct, then IgA may act as a blocking factor with respect to the developement of gold-induced toxicity or hypersensitivity. A decrease in blocking factor may then facilitate development of toxicity or hypersensitivity. In this respect it may be relevant that a qualitative defect in IgA production in patients with atopic allergy is associated with overstimulation of IgE production (12). A blocking action of IgA could also explain the fact that, at resumption of gold therapy after toxicity has disappeared, toxicity generally does not reappear as quickly as might be expected in the case of mere hypersensitivity. The explanation may be that, after stopping gold therapy, IgA levels increase, as we have observed (data not shown), and thus form a new blocking barrier.

Monitoring of gold-induced toxicity at this time depends on regular clinical evaluation, haematological screening and urinalysis. Prediction of gold toxicity at the present state

of the art remains virtually impossible. Monitoring of serum- or cell-bound gold concentrations has been disappointing in this respect (13,14,15). Peripheral blood eosinophilia sometimes precedes toxicity, but this remains unreliable (16). The association of drug toxicity and certain HLA antigens (2,3,4,5) points to a high-risk group with respect to toxicity but is of little practical value for the individual patient. The present data have to be extended by further studies before definite conclusions can be drawn about their value in predicting toxicity. Our data suggest, however, that patients with subnormal serum IgA are at particular risk and may be future candidates for drug dose reduction once IgA becomes subnormal.

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CHAPTER 5

IgA DEFICIENCY DURING AUROTHIOGLUCOSE TREATMENT

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Submitted for publication

INTRODUCTION

Selective IgA deficiency is the most common permanent primary immune deficiency, estimated to occur in the normal population at a rate of one in 500 to 700. Drug-induced selective IgA deficiency has been described for phenytoin (1,2), D-penicillamine (3,4) and aurothiomalate (5). This report discusses IgA deficiency developing during treatment with aurothioglucose of a patient with seronegative rheumatoid arthritis. Immunological data would suggest a defect in IgA secretion rather than in manufacturing by plasma cells.

CASE REPORT

The patient was a 43-year-old woman, with a 15 year history of polyarthritis, who was seen at the out-patient clinic with signs of exacerbation. She had previously been treated with hydroxychloroquine and non-steroidal anti-inflammatory drugs. Physical examination revealed signs of active polyarthritis without extra-articular manifestations. Laboratory data were as follows: ESR 12 mm after one hour, haemoglobin 7.7 mmol/l, normal peripheral blood, leucocytes, differential count and hepatic and renal function tests. Serum immunoglobulins: IgA 2.29 g/l, IgG 12.45 g/l and IgM 0.93 g/l (normal values for IgA, IgG and IgM are (mean $\pm$ SD) 2.0 $\pm$ 0.6, 12.5 $\pm$ 2.1 and 1.1 $\pm$ 0.4 g/l, respectively); the Waaler-Rose, latex fixation test and ANA were negative. The complement factors were within the normal range; no circulating immune complexes were demonstrable by the C1q binding assay. Treatment with aurothioglucose was started: after a test dose of 10 mg, weekly injections of 50 mg were given. After a cumulative dose of 460 mg aurothioglucose, the patient developed generalized dermatitis and stomatitis. In spite of dose reduction these symptoms exacerbated and soon made it necessary to stop gold injections. At that time the laboratory findings were as follows: ESR 10 mm after one hour, haemoglobin 7.4 mmol/l. Platelets 329 x 10^9/l and leucocytes 6.5 x 10^9/l with a normal

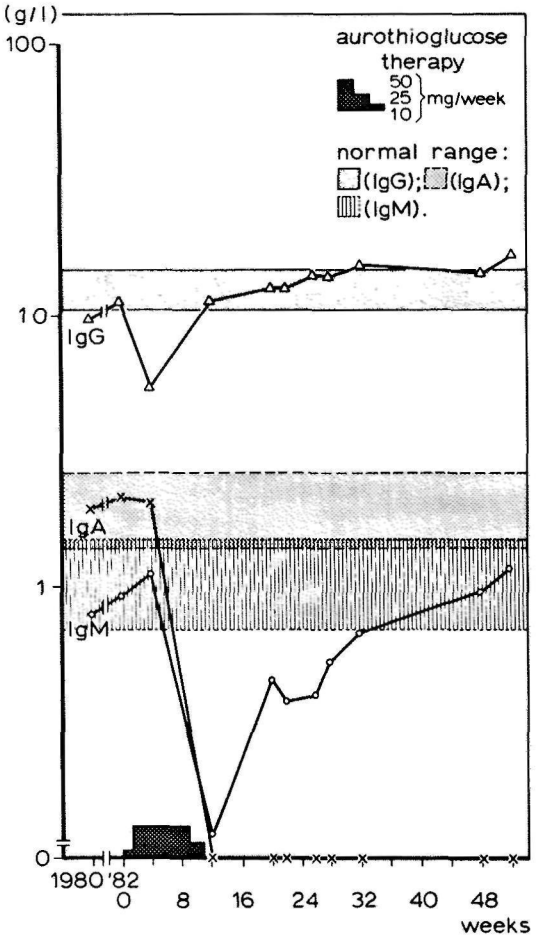

Figure 1. Immunoglobulin levels in relation to aurothioglucose treatment

differential count without eosinophilia. Hepatic and renal function tests were normal and the Waaler-Rose test and latex fixation test were negative. However, ANA had become positive, as had the C1q binding assay (7%). Serum immunoglobulins as detected by radial immunodiffusion revealed undetectable IgA levels (less than 0.02 g/l) IgM below normal (0.11 g/l) and a normal IgG (11.47 g/l) (see also figure 1). Gold therapy was stopped and serum immunoglobulins, ANA and C1q binding were regularly determined. The serum IgA level continued to be undetectable during a 9-month follow-up period, whereas IgM and

IgG serum levels gradually increased (figure 1). The C1q binding assay became negative again, but the ANA remained positive. During the follow-up period the patient developed no signs or symptoms associated with IgA deficiency, i.e. gastrointestinal or pulmonary abnormalities.
Additional immunological studies revealed that the patient had no detectable antibodies against IgA in the serum and no secretory IgA in the saliva. Lymphocyte stimulation tests using Concanavalin A, PHA and PWM as well as specific stimuli including PPD, candida, trichophyton, mumps and varidase gave normal values. Immunofluorescence studies of a biopsy specimen from the small intestine revealed normal numbers of IgA, IgM and IgG-positive plasma cells.

DISCUSSION

The patient described developed selective IgA deficiency during treatment with aurothioglucose. To our best knowledge this is the first description of IgA deficiency during treatment with this drug. The other patient developing gold-associated IgA deficiency was treated with aurothiomalate (5).
Theoretically, IgA deficiency can result from either decreased IgA synthesis or an increased loss or catabolism of IgA. Although we cannot rule out the latter possibility completely, it seems unlikely that this was involved in our patient. To begin with, antibodies against IgA could not be detected. In addition, if increased loss of IgA were the cause of the deficiency it would likely have been accompanied by persistent low levels of the other immunoglobulins, which was not the case. In fact, a defect in IgA synthesis or secretion by plasma cells seems much more likely.
It has been reported that a deficiency of serum IgA is often accompanied by a deficiency of secretory IgA (6). The absence of secretory IgA in the saliva strongly suggests that this was also the case in our patient. On the other hand the immunofluorescence data on the small intestine indicate that plasma cells in the lamina propria were able to synthesize IgA. This

observation would suggest that the IgA deficiency of our patient was probably due to a defect in IgA secretion rather than in manufacturing by the plasma cells. The mechanism of this defect is unknown, but published data show a striking association between selective IgA deficiency and disorders of the T-cell system (7,8). One possibility may therefore be that aurothioglucose affects immunoglobulin production at the T-cell level, as suggested for D-penicillamine (9). Our data showing normal lymphocyte function test values, are not necessarily in disagreement with this observation.

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CHAPTER 6

LOOSE STOOLS DURING AURANOFIN TREATMENT: CLINICAL STUDY AND SOME PATHOGENETIC POSSIBILITIES

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SUMMARY

Loose stools, one of the most frequent adverse reactions ascribed to the orally absorbed gold compound auranofin, was studied during a long-term trial. At some time during the study 44% of the patients reported the occurrence of loose stools. No infective cause or signs of malabsorption were found; nor were loose stools caused by the presence of osmotically active substances in the gut lumen. Arguments for a direct effect of auranofin on the ion and water absorption in the intestine are given. Although no morphological studies on biopsy material are available, the proven side effect of the drug does not seem to necessitate discontinuation of treatment in patients as toxic to gut function.

INTRODUCTION

Gold compounds have been used in the treatment of rheumatoid arthritis since 1928 (1,2). Several double blind studies have demonstrated their therapeutic value. However, the drugs frequently give rise to adverse reactions (3,4,5). Approximately 80% of such reactions comprise rashes, pruritus, stomatitis and mild proteinuria. Although adverse reactions involving the gastro-intestinal tract are rare, they are usually serious; gold-induced enterocolitis has been reported and in more than 50 percent of these patients ended fatally (6,7). Since Finkelstein et al. (8) reported in 1976 that auranofin, an orally absorbed gold compound, was well-tolerated and effective as an antirheumatic drug as well, many studies on auranofin have been done in different countries. Unlike the intramuscularly administered gold salts, auranofin seldom caused rash, pruritus, stomatitis and proteinuria, but gastrointestinal symptoms, mostly loose stools, were frequently observed. In this report we present data on this adverse reaction during a long-term trial with auranofin.

PATIENTS AND METHODS

Patients. In October 1980, a one-centre patient blind study comparing auranofin and aurothioglucose was started. All patients had definite or classical rheumatoid arthritis according to the criteria of the American Rheumatism Association (9). The clinical and laboratory characteristics of the patients on auranofin are given in table I. All patients were treated with non-steroidal anti-inflammatory drugs (NSAID) simultaneously with the gold therapy; no other medication was allowed. Patients on aurothioglucose started with a test dose of 10 mg, followed by 50 mg weekly up to a cumulative dose of 1000 mg. The dose was then reduced to 50 mg every 2-4 weeks. Patients on auranofin received 6 mg as a single morning dose daily throughout the study. Patients were randomly allocated to either auranofin or aurothioglucose. None of the patients

Table I. Clinical and laboratory characteristics of the patients with and without loose stools. Mean ± SD and (in parentheses) range are given.

	loose stools	normal stools
Number and sex of patients	11; 10F - 1M	14; 7F - 7M
Age (yrs)	41 ± 14 (25-68)	53 ± 10 (38-66)
Seropositive	10	11
ESR (mm after 1 h)	61 ± 41 (23-112)	62 ± 38 (14-147)
Hb (mmol/l)	7.1 ± 0.8 (5.8-8.0)	7.7 ± 1.2 (5.6-9.3)
Serum gold (µg/100 ml)	63 ± 31 (40-97)	57 ± 29 (35-125)

had had gastro-intestinal disease or symptoms before the study. To minimize the influence on the bowel habits, the patients were asked to make no deliberate change in their diet during the study.

Examinations of patients with loose stools. If a patient reported loose stools lasting more than one week, the following examinations were performed: plasma electrolytes, serum cholesterol, stool examination for pathogenic flora, ova and parasites, occult blood and Sudan III staining to note the presence of excess fat. In accordance with the protocol of the trial the following examinations were also performed: hemoglobin, platelets, white blood cell count and differential smear, serum iron, total proteins and blood sugar. Serum gold levels were assessed by atomic absorption spectroscopy using a Perkin-Elmer model 5000 with a graphite furnace (Perkin-Elmer, HGA 400). Samples for serum gold level determination were taken between 13.00 hrs and 16.00 hrs at visits to the outpatient clinic.

Earlier experiments at our department had revealed a flat serum level versus time curve throughout the day for the oral gold when a plateau level of gold had been reached approximately at week 8 of treatment.

In three patients with daily loose stools for a period of se-

veral weeks or longer, total daily stools were collected for two days during treatment and for three days after oral gold therapy had been stopped. In these three patients the following examinations were also performed during treatment: D-xylose test, vitamin B12 absorption test (Schilling test), a glucose breath test, the total daily stool weight (wet and dry), sodium and potassium content of the feces and osmolality measurements of the stools. Feces for osmolality measurements were collected in plastic bags and immediately stored at -20°C until analyzed. For analysis the stool was thawn, homogenized and, if necessary, diluted with sterile water.

Definitions. Loose stools were defined as a relative increase in frequency of bowel movements and in fluidity of feces as compared with the usual bowel habit of the same individual, the daily wet weight of the stools is usually not in excess of 400 g.
Osmotic diarrhea was defined according to Fordtran (10) as stools having an osmolality far in excess than twice the sum of the concentrations of sodium and potassium in the stool water. The osmolality of fecal fluid in normal subjects obtained by high speed centrifugation is, according to Wrong (11): 475 $\pm$ 66 mosmol/kg; it contains 32 $\pm$ 19 mmol/l sodium and 70 $\pm$ 33 mmol/l potassium (mean $\pm$ SD).

RESULTS

Clinical findings. Of the 26 patients treated with aurothioglucose, only one experienced a period of loose stools for more than one week, starting after return from vacation. Of the 25 patients on auranofin, 11 had loose stools for a longer period at some time during treatment (figure 1). The frequency of loose stools varied from one to eight times a day. However, the occurrence of symptoms during treatment was not a constant phenomenon in all patients; three of the eleven patients had loose stools on only 3-4 days a week and normally formed feces on the other days. All patients reported abdominal cramps,

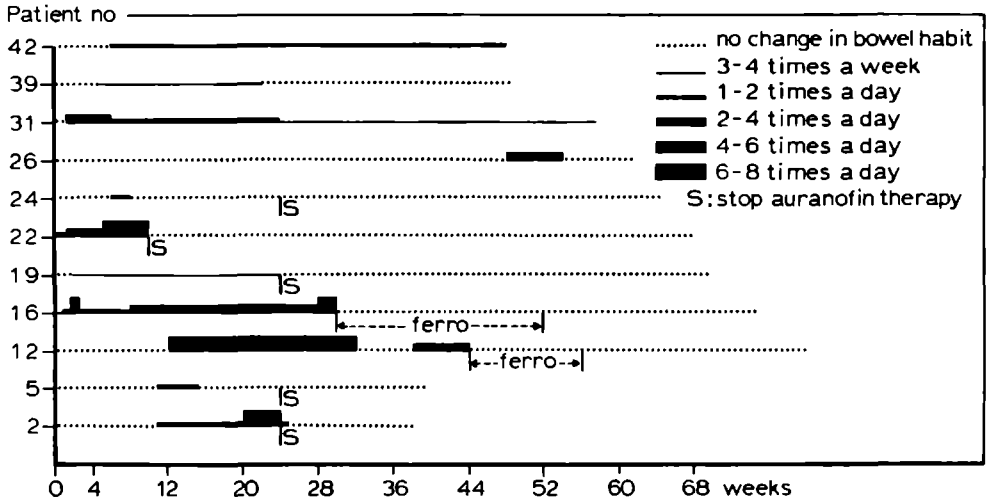

Figure 1. Data on the onset, duration and intensity of loose stools in the auranofin treated patients.

occurring mostly in the first hours after the ingestion of the tablets, and they were free from these symptoms after passing the stools. None of the patients experienced loose stools in the evening and during the night.One patient (no.22) with loose stools, often of watery consistency, and episodes of abdominal cramps six to eight times a day, dropped out. This resulted in prompt discontinuation of the production of the loose stools, and the patient regained her original bowel habits, i.e. once per three days. Rechallenge in this case was not performed. In four other patients (nos. 2,19,26,31) who dropped out for other reasons, loose stools likewise ceased within a few days after withdrawal of the drug.

Influence of ferro medication on loose stools. In two patients the loose stools stopped immediately after introduction of a concomitant ferro preparation for iron deficient anemia. Although this medication was discontinued later on, these two patients regained their normal bowel habit of the period before the gold treatment was started. The auranofin treatment

was not changed in the whole period.

Laboratory data. In all patients the plasma electrolytes, total protein, blood sugar and serum cholesterol showed no abnormalities. There was no pathological flora in the stool cultures. Examination for occult blood and Sudan III staining for evidence of steatorrhea were also negative. In the three patients studied more extensively, the D-xylose test, the Schilling test and the glucose breath test were normal. The total daily stool weight (wet) and the osmolality measurements were also within normal limits. However, aberrant values for stool electrolytes and dry weight of feces were found. As shown in figure 2, patients with loose stools had higher stool sodium concentrations than those without loose stools. In contrast, potassium concentrations were lower in patients with loose stools than in those without loose stools. The stool electrolytes and dry weights of the three patients studied extensive-

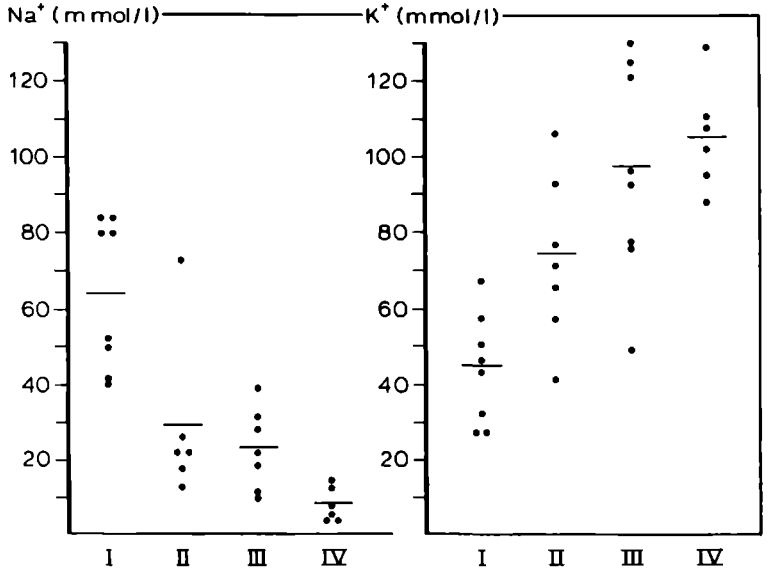

Figure 2. Values of stool electrolytes in auranofin treated patients with and without loose stools (I and II respectively) and patients treated with intramuscular gold and normal controls (III and IV respectively).

Table II. Stool electrolytes and stool dry weights in the three patients studied during and after the auranofin medication.

patient no.	during treatment			after withdrawal of treatment		
	Na^+ (mmol/l)	K^+ (mmol/l)	dry weight* %	Na^+ (mmol/l)	K^+ (mmol/l)	dry weight %
1	84	43	8	10	57	30
2	41	58	18	8	78	26
3	50	47	17	6	75	23

* Dry weight is expressed as the percentage of the wet weight of the stools after freeze drying.

ly are given in table II. After discontinuation of treatment, the values were normalized. During the study, changes in body weight or change in serum gold level in relation to the occurrence of loose stools were not observed.

DISCUSSION

Auranofin, a new orally absorbable gold compound, is under investigation in many countries for its efficacy and safety in the treatment of rheumatoid arthritis. We studied the most frequent adverse reaction to this drug, the occurrence of loose stools, in order to determine its clinical characteristics and its possible underlying mode of action.

Rheumatoid patients are often less mobile than healthy people; this lack of activity may at least partly be responsible for their reported tendency to constipation. In this respect loose stools are a welcome extra-effect of the drug; on the other hand, in terms of toxicology, the phenomenon could be a sign of serious and unacceptable damage, necessitating discontinuation of the drug, at least in the individual, or even removal of the drug from the market. Recently, several algorithms have been published (12,13,14) for assessment of the probability of adverse drug reactions. In order to establish whether there is

a causal relationship between loose stools and auranofin administration, we applied the simple method for estimating the probability of adverse reactions described by Naranjo et al. (12). According to their method, loose stools was classified as a definite adverse reaction to auranofin.

In this report we demonstrate that 44% of the patients on auranofin experienced abdominal cramps and loose stools at some time during the treatment. This side-effect did not occur at a specific time after starting the drug. Some patients experienced it immediately after medication was started; in other patients it appeared only after they had taken the drug for several months.

Loose stools is sometimes a transient phenomenon: some patients regained their normal bowel habit after some time, although no change in medication had taken place. An infective cause or signs of malabsorption have not been found in these patients. Since the serum gold levels were not different in the auranofin-treated patients with or without loose stools, gold absorption was not affected. We also demonstrated in this study that the loose stools were not the consequence of the presence of unusual amounts of non absorbable, osmotically active substances in the gut lumen: the osmolality of the feces was normal. The clues to a direct effect of auranofin on the gut mucosa to be considered were:

a. the lack of correlation between the serum gold level and the occurrence of loose stools.

b. time relationship: most of the patients complained of abdominal cramps and loose stools in the first 3-4 hours after ingestion of the tablets.

c. effect of stopping auranofin: immediately after stopping the medication, the loose stools nearly always disappeared.

d. effect of dose reduction: disappearance of the loose stools has been observed after reducing the dose of auranofin medication or dividing the dose over the day (15).

The data on the stool electrolytes in patients with loose stools indicate a net accumulation of fluid and electrolytes

in the intestine. These changes may be brought about either by inhibition of ion and water absorption or by stimulation of fluid secretion, or by a combination of both. Mechanisms involved could be: an increase in mucosal permeability, alteration in active ion transport processes or increase in mucosal cyclic AMP. A comparable effect has been seen with several laxatives like ricinoleic acid (16,18), dioctyl sodium sulfosuccinate (19,20) and bisacodyl (21,22). The action of these drugs, however, also results in increased potassium secretion (which has not been found with auranofin). A direct effect on intestinal motor activity is another possibility in the pathogenesis of loose stools in these patients; however, a causal relation between increased motility and diarrhea has never been established (23). Recently, a laxative-like effect of NSAID was reported (24), causing accumulation of fluid by mucosal membrane damage. All our patients, whether they used aurothioglucose or auranofin and whether they had loose stools or not, used NSAID concomitantly. Therefore these drugs cannot explain the occurrence of loose stools in these patients. Additional information, especially a direct study of the influence of auranofin on the intestinal absorption of water and electrolytes, is therefore required in order to determine the pathogenesis of the fluid and electrolyte accumulation in the gut lumen as the side effect of the drug. We felt it was not justifiable to submit the patients with loose stools to endoscopic examination with biopsy of the gut mucosa, since the non invasive examinations revealed nothing suggestive of malabsorption or a major defect of mucosal permeability. Still we believe we have demonstrated that loose stools is a proven side-effect of auranofin and that, in view of the present data, this does not seem to necessitate discontinuation of treatment in the individual patient or removal of the drug from the market as toxic to gut function.

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CHAPTER 7

MONITORING SERUM GOLD LEVELS DURING TREATMENT WITH AURANOFIN AND AUROTHIOGLUCOSE

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SUMMARY

Serum gold levels were measured in the context of a clinical trial, both in patients treated with the parenterally administered gold compound aurothioglucose and in patients treated with a new orally absorbable gold compound auranofin. No correlation was found between the serum gold level and the degree of response nor toxicity on aurothioglucose and auranofin. A statistically significant decline in the serum gold level after one year ($p < 0.05$) was found in patients treated with auranofin, probably not due to insufficient patient compliance; it is suggested that a shift from protein-bound gold to cell-bound gold is the explanation of this.

INTRODUCTION

Since the introduction of gold compounds in the treatment of rheumatoid arthritis, several attempts have been made to find pharmacokinetic parameters to improve drug efficacy, while minimizing undesirable side effects (1-8). Reports on the question whether serum gold levels correlate with clinical response have so far been contradictory. Scoring individual responses to gold treatment in the context of a clinical trial, we decided to make another attempt to correlate serum gold levels with the degree of response to aurothioglucose as well as to auranofin, a new orally absorbable gold compound (9). The clinical trial compared the efficacy and toxicity of the two drugs. From the literature we know that toxic and non-toxic patients treated with parenterally administered gold compounds do not differ in serum gold levels (4). However, with respect to the most frequent adverse reaction to auranofin treatment, i.e. loose stools, no evidence is yet available as to whether serum gold levels in patients with loose stools differ from those in patients without loose stools.

METHODS

Patients. Fifty-two patients with active classical or definite rheumatoid arthritis according to the revised ARA criteria (10) were selected for a single blind 52-week study comparing the efficacy and safety of auranofin and aurothioglucose. No concomitant medication for rheumatoid arthritis was allowed, except non-steroidal anti-inflammatory drugs. Clinical characteristics of these patients, admission criteria, types, course and frequency of gold toxicity during the first year of treatment are described elsewhere (9).

Gold medication. Patients on aurothioglucose (20% oily suspension, Noury-Pharma, Oss, The Netherlands) received 50 mg aurothioglucose per week by intramuscular injection up to a cumulative dose of 1000 mg; thereafter the injections were given

every two weeks up to a cumulative dose of 1500 mg, after which 50 mg was given every three weeks until the end of the study. Patients on auranofin (SK&F, The Hague, The Netherlands) received 6 mg daily as a single morning dose throughout the study.

Criteria of response. Patients were divided into excellent, moderate and non-responders, using a newly developed method (11) which included the degree of improvement as well as the degree of disease activity attained; this method was adapted from the activity index described by Mallya et al. (12).

Adverse reactions. Patients were considered to have developed adverse reactions probably due to the gold compound, if no alternative cause for the observed reaction was found and if clearance or diminution of the adverse reaction was seen after cessation of treatment. Fourteen patients treated with aurothioglucose had severe adverse reactions in the course of a 12-month follow-up, necessitating suspension or discontinuation of treatment. Thirteen of these patients had generalized dermatitis (one had stomatitis, another had proteinuria at the same time) and one patient had a polyneuropathy. Only two auranofin-treated patients had severe adverse reactions necessitating discontinuation of treatment (dermatitis, diarrhoea). Eleven patients reported the occurrence of loose stools during auranofin treatment.

Collection of blood samples and gold analysis. Blood samples were collected at 2-month intervals prior to the next injection. Whole blood was collected in stoppered plain vacutainer tubes. Serum was obtained by centrifuging at 1000 g for 20 minutes and was stored frozen until analysed. Serum gold levels were assessed by atomic absorption spectroscopy (Perkin-Elmer, model 5000) with a graphite furnace (Perkin-Elmer, HGA 400) (13). The reproducibility of gold determination in serum at a concentration of 50 µg/100 ml was expressed as coëfficient of variation, and turned out to be less than 3%.

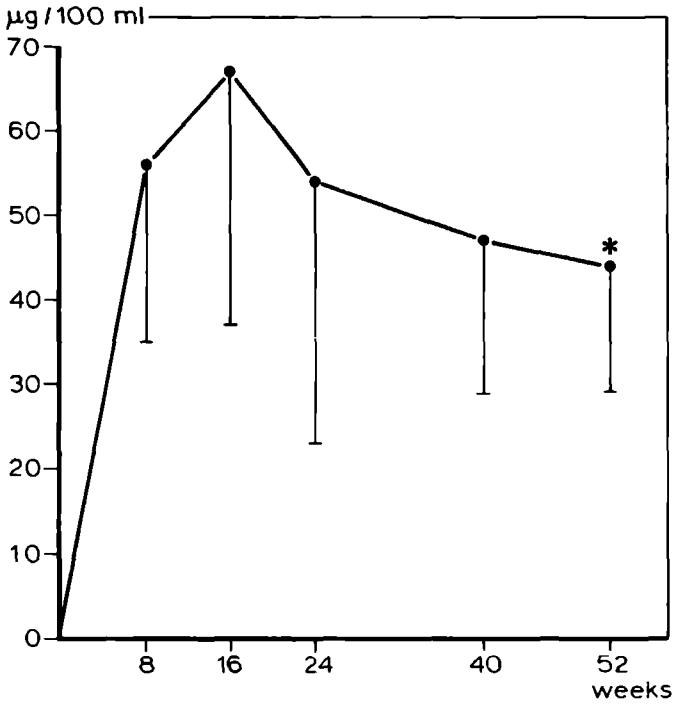

Figure 1. Course of the serum gold level in eleven auranofin-treated patients

RESULTS

Course of the serum gold levels. The serum gold level in the aurothioglucose-treated patients reached a plateau level and then declined in proportion to the reduction of the administered gold dose. In the auranofin-treated patients a plateau serum gold level was reached after 16 weeks of treatment. Despite constant dosing, a gradual decline in serum gold level was observed thereafter in the patients treated for at least one year; it was statistically significant at week 52 ($p < 0.05$, paired t-test; figure 1). The patients withdrawn during the first year of treatment showed a similar decline in serum gold level. Their serum gold levels (mean $\pm$ SD) at week 16 and 24 were 59 $\pm$ 25 µg/100 ml and 51 $\pm$ 16 µg/100 ml, respectively

Table I. Serum gold levels (µg/100 ml, mean ± SD) arranged according to degree of response in auranofin- and aurothioglucose-treated patients; n = number of patients.

Therapy	AURANOFIN									AUROTHIOGLUCOSE								
weeks of	*excellent*			*moderate*			*no*			*excellent*			*moderate*			*no*		
therapy	response			response			response			response			response			response		
	M	SD	n	M	SD	n	M	SD	n	M	SD	n	M	SD	n	M	SD	n
8	62	± 23	5	67	± 34	6	52	± 22	12	319	± 109	9	259	± 100	7	229	± 75	5
16	72	± 41	5	79	± 26	6	56	± 21	11	333	± 68	9	259	± 57	7	270	± 95	5
24	72	± 48	5	51	± 19	6	46	± 14	11	240	± 103	7	198	± 62	7	201	± 78	4
40	55	± 24	5	36	± 13	3	44	± 8	5	191	± 82	5	162	± 57	5	-		
52	54	± 17	5	34	± 11	3	39	± 4	3	117	± 17	5	158	± 93	5	-		

Table II. Serum gold levels (µg/100 ml, mean ± SD) in patients with and without toxic reactions to auranofin and aurothioglucose; n = number of patients.

Weeks of therapy	AURANOFIN						AUROTHIOGLUCOSE					
	loose stools			no loose stools			toxic group			non-toxic group		
	M	SD	n	M	SD	n	M	SD	n	M	SD	n
8	63	± 31	11	57	± 29	12	279	± 38	11	241	± 104	11
16	70	± 23	10	58	± 31	12	293	± 69	10	264	± 83	11
24	54	± 14	10	50	± 29	12	224	± 37	7	215	± 95	11
40	49	± 12	4	46	± 19	9	211	± 36	3	166	± 71	8
52	46	± 14	4	44	± 17	7	136	± 71	3	169	± 83	8

(0.05 < p <0.1, paired t-test).

Therapeutic response: correlation with serum gold levels. No significant differences in serum gold levels were found between excellent, moderate or non-responders to aurothioglucose and auranofin treatment (table I).

Adverse reactions: correlation with serum gold levels. No differences were found in the serum gold levels of aurothioglucose-treated patients with and without adverse reactions. The auranofin-treated patients with and without loose stools (table II) showed no significantly different serum gold levels.

DISCUSSION

Although it has been possible to measure serum gold levels by atomic absorption spectroscopy for more than 14 years, reports on whether or not serum gold levels correlate with clinical response to parenterally administered gold compounds are still contradictory (1-8) Some investigators advocate an individualized gold therapy regimen with maintenance of serum gold levels between 300-400 µg/100 ml during aurothiomalate treatment in order to obtain a favourable response (6). In this study we found no correlation between the individual serum gold levels and response to aurothioglucose treatment. Due to the gradual decline of the gold dose in the aurothioglucose-treated patients, the excellent responders as well as the moderate responders in our study had far lower serum gold levels than those advocated by Lorber (6). In the auranofin-treated patients we did not find a correlation between serum gold level and therapeutic response either.

In agreement with the literature we found no differences in serum gold levels between toxic and non-toxix aurothioglucose-treated patients. As already suggested by us elsewhere on the basis of preliminary data, no differences were found in the course of the serum gold levels between patients with and

without loose stools on auranofin treatment (14). No other reports on the absence of this relationship exists.

Surprisingly, we found that most auranofin-treated patients showed a spontaneous decline of the serum gold level after the plateau had been reached. It was evident from the return tablet count that this decline was not related to insufficient patient compliance. Sixty-three percent (5 out of 8) of the patients with an excellent or moderate response after 10 months of treatment showed a decline in serum gold level, while only 20% (1 out of 5) of the non-responders did so at that time ($p = 0.1$, Fisher exact test). Since other investigators found stable whole blood gold concentrations during long-term treatment with auranofin, this decline in serum gold level may be due to a shift from protein-bound gold to cell-bound gold; in fact we did not measure the amount of gold bound to cellular blood constituents in a systematic longitudinal way.

In summary we have shown the following:

1. No correlation exists between serum gold levels and therapeutic response to either auranofin or aurothioglucose treatment. Our excellent responders to aurothioglucose treatment had far lower serum gold levels than those advocated by Lorber.
2. Patients with loose stools on auranofin treatment did not differ in serum gold levels from patients without loose stools.
3. Most patients showed a decline in serum gold levels during long-term treatment with auranofin; this was statistically significant after one year. We conclude that this finding stresses the need to measure whole blood gold concentrations as well as serum gold concentrations in future studies, because this decline in serum gold level may be due to a change in the distribution of the gold compound.

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CHAPTER 8

CELL-BOUND GOLD (CBG) IN PATIENTS TREATED WITH AUROTHIOGLUCOSE AND WITH AURANOFIN. A COMPARISON OF DIFFERENT METHODS OF DETERMINATION

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SUMMARY

Three different methods of determining the cell-bound gold concentration were compared in patients given intramuscular and oral chrysotherapy for rheumatoid arthritis. We found a strong correlation between the different methods, and no difference between two washing procedures.

INTRODUCTION

Gold salts have been used in the treatment of rheumatoid arthritis since 1928 (1-2). Many efforts have been made to study the correlation between gold pharmacokinetics and clinical effect and toxicity, in order to improve drug efficacy and minimize undesirable side-effects.

Pharmacokinetic parameters which have been demonstrated to have no or contradictory correlations with pharmacodynamics include plasma and serum gold levels (3-6), binding of gold to non-albumin serum proteins (7), total body gold retention and urinary gold excretion (8,9). Recently, a correlation has been suggested between the gold concentration in erythrocytes and the incidence of toxic reactions (10), although other authors reported absence of this correlation (7). These contradictory results may at least partly be due to different procedures of washing erythrocytes and different methods to determine the cell-bound gold (CBG) concentration.

Auranofin, an orally absorbable gold compound, has been found to be associated with erythrocytes in a greater extent than the intramuscularly administered gold salts (11). We decided to compare the different methods of determining CBG described in the literature in the context of a single blind study on auranofin versus aurothioglucose in patients with rheumatoid arthritis. This report presents the findings of two different washing procedures and three different ways of determining the CBG concentration, and describes the influence of storage of blood samples at room temperature.

MATERIALS AND METHODS

Patients and schedule of gold administration. The patients (8 on aurothioglucose and 11 on auranofin) had a definite or classical rheumatoid arthritis fulfilling the criteria of the American Rheumatism Association (12). The usual parameters

Table I. Characteristics of the patients treated with auranofin and aurothioglucose, respectively; mean ± SD and (in parentheses) range are given*

	auranofin	aurothioglucose
Number and sex of patients	11; 6F-5M	8; 5F-3M
Age (yr)	54±11 (38-67)	64±10 (41-69)
Seropositive	7	5
ESR (mm after 1 h)	26.7±19.2 (12-62)	27.4±20.4 (9-66)
Hb (g/100 ml)	12.6±1.0 (11.4-14.0)	12.7±1.3 (11.1-14.7)
Erythrocyte count (10^{12}/l)	4.31±0.38 (3.71-4.80)	4.27±0.26 (3.71-4.87)
Plasma gold (µg/100 ml)	47.6±24.3 (31-98)	112.6±49.2 (40-178)
CBG (µg/100 ml)	20.5±3.7 (15-25)	6.0±7.7 (0-19)

* Figures on cell-bound gold (CBG), obtained by the direct method.

for assessing therapeutic response in rheumatoid arthritis were measured. Only medication with non-steroidal anti-inflammatory drugs was allowed simultaneously with gold therapy. Clinical and laboratory characteristics of these patients are given in table I. In some patients, not all determinations to be described could be made. Auranofin was provided by SK&F, The Hague, , The Netherlands; the intramuscularly given gold salt was aurothioglucose (20% oily suspension, Noury Pharma, Oss, The Netherlands). Patients on aurothioglucose started with a test dose of 10 mg, after which 50 mg weekly was given up to a cumulative dose of 1000 mg, thereafter the dose was reduced to 50 mg every 2-4 weeks. Patients on auranofin received 6 mg daily as a single morning dose with breakfast throughout the study. Blood samples were taken from patients receiving the drugs for at least six months. All patients treated with aurothioglucose included in this study, got their injections at fortnightly or longer intervals.

Collection and preparation of samples for gold assay. Blood samples from patients on aurothioglucose were collected prior to the next injection. Venipunctures were made between 1.00 and 4.00 p.m.; patients on aurothioglucose were given their injection of the drug just after venipuncture. Blood was collected in stoppered calibrated heparinized tubes and the haematocrit value was measured and an erythrocyte count was made. For washing procedure I the erythrocytes were separated from the plasma by centrifuging at 1000 g for 20 minutes. The isolated erythrocytes were washed 5 times with sterile isotonic saline; after this the cells were suspended in saline up to original blood volume (giving sample I) and an erythrocyte count was made. For washing procedure II a centrifugation pellet of erythrocytes was washed twice with Hymans' washing medium (13) and suspended with saline up to the original blood volume (giving sample II). An erythrocyte count was also made. Finally, some blood was immediately stored at -20°C until measurement. The samples I, II and III were likewise stored frozen until measurement. Some blood was kept at room temperature and processed the next day, using the washing procedure with saline (giving sample III); storage of a sample outside the refrigerator is probably not uncommon in a hospital situation. The amount of erythrocyte loss caused by the washing procedures proved to be less than 5%. The coëfficient of variation of the haematocrit determination and erythrocyte counts was 2%.

Method of gold determination. Gold levels in plasma, erythrocytes, whole blood and washing fluid were assessed by atomic absorption spectroscopy (Perkin-Elmer, model 5000), with a graphite furnace (Perkin-Elmer, HGA 400); Sheathing gas, purified nitrogen (flow rate = 450 ml/min). Instrument settings: spectrophotometer 242.8 nm, integration time 5 sec, slit width 0.7 nm, hollow cathode lamp (10 mA). Background: deuterium lamp. Thermal treatment: drying at 120°C, hold time 20 sec; ashing at 900°C, hold time 30 sec; atomization at 2400°C, hold time 10 sec. Stop flow during atomization. Measurements were

Table II. Reproducibility of gold determinations at various concentrations (30, 50 and 150 µg/100 ml) of gold chloride added to plasma or whole blood, expressed as coefficient of variation of 10 measurements.

µg/100 ml	coefficient of variation (percent)	
	plasma	whole blood
30	4.9	6.8
50	2.8	3.4
150	2.4	2.4

made by comparison of the absorbance peaks. The standard solutions were prepared from a stock solution (gold chloride 1 mg/ml, BHD, Buschwig, Amsterdam, The Netherlands). This solution was diluted either with a 20% albumin solution or whole blood depending on the sample, in concentrations of 5-10-15-20-30-50-75-100-150 µg/100 ml. 10 µl of a sample was injected.

Methods of determining CBG. A. CBG expressed in absolute terms (concentration in cell suspension made by suspending the erythrocytes washed with saline up to the original blood volume (direct method).B. CBG expressed as amount of gold in $10x10^{12}$ erythrocytes per litre, washed with saline; this was done to compare our results with data from the literature (direct method). C. CBG calculated by subtracting the plasma gold concentration corrected fro haematocrit from the whole-blood gold concentration (indirect method).
The coefficient of variation of 10 determinations at the respective gold concentrations in whole blood and plasma are shown in table II. The error in CBG measurements made by method C due to multiplying and subtracting different figures with their respective coefficient of variation, was comparable with the error made by the different washing procedures; both were in the order of 6%.

Ethical aspects. Patients had given informed consent for the

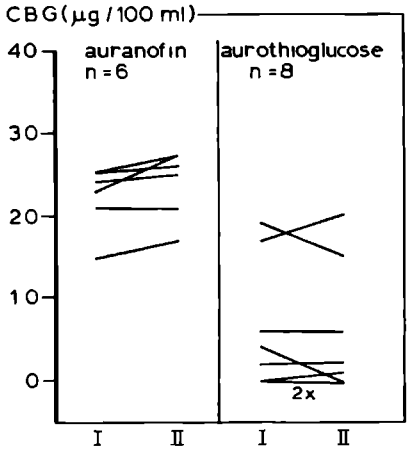

Figure 1. CBG determined after the two different washing procedures (sample I:saline; sample II:Hymans' solution) in both treatment groups.

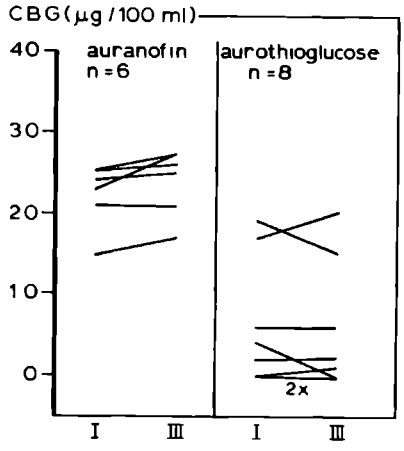

Figure 2. CBG determined after instantaneous processing (I) and after storage of the blood sample for one day at room temperature (III) for both treatment groups.

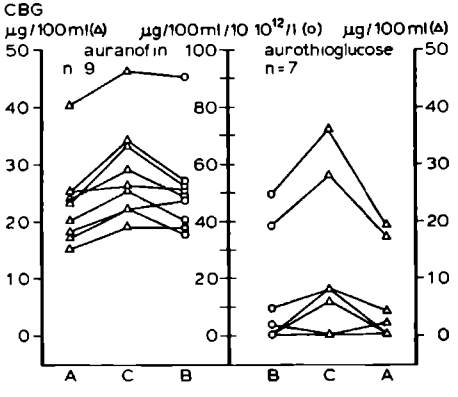

Figure 3. Comparison between CBG determined by three different methods.
A. Direct method, CBG expressed in µg/100 ml.
B. Direct method, CBG expressed in µg/100 ml in $10x10^{12}$/l erythrocytes.
C. Indirect method, CBG expressed in µg/100 ml.

drug trial; the Hospital Ethics Committee had given approval to the protocol.

RESULTS

The CBG values determined with the two washing procedures and expressed in absolute terms (samples I and II) are equal; this applies to both treatment groups. Figure 1 illustrates the findings in the individual patients. In the auranofin-treated patients the mean ± SD for sample I is 20.5 ± 3.7 µg/100 ml; and for sample II it is 20.5 ± 2.9 µg/100 ml, respectively. In the aurothioglucose-treated patients it is 6.0 ± 7.7 µg/100 ml for sample I, and 5.0 ± 8.0 µg/100 ml for sample II.
Storage of a whole blood sample at room temperature for one day does not influence the CBG in the aurothioglucose-treated patients; mean ± SD for sample I: 6.0 ± 7.7 µg/100 ml for sample III: 5.5 ± 7.8 µg/100 ml (figure 2).
In the auranofin treated patients there is a slight but statistically significant increase in CBG ($p < 0.05$, paired t-test); mean ± SD for sample I: 22.2 ± 3.8 µg/100 ml; sample III: 23.8 ± 4.0 µg/100 ml. The three different methods of calculating the CBG correlate well (figure 3). Method B with method A: $r = 0.93$; method C with method A: $r = 0.96$. The amount of gold in the washings ranges from 2 to 17% in the auranofin-treated patients from 0 to 16% in the aurothioglucose-treated patients. Comparison of the calculated CBG (method C) with the CBG expressed in absolute terms of non-washed erythrocytes reveals no difference. The amounts of gold in the erythrocytes (samples I, II and III), whole blood and plasma as well as data about the smoking habits of the individual patients are given in table III. The CBG values of smokers in the auranofin group were not higher than in the non-smokers of that group. The two patients in the aurothioglucose group with the highest CBG levels smoked cigarettes, in another patient, who smoked cigarettes, no detectable CBG was found.

Table III. Gold concentrations, erythrocytes, haematocrits, and smoking habits of 11 patients treated with auranofin, and 8 patients treated with aurothioglucose.

patient no.	erythrocytes	haematocrit	samples			whole blood	plasma	smoker
	$10x10^{12}/l$	l/l	I	II	III	µg/100 ml	µg/100 ml	
auranofin								
1	3.84	0.38	18	18	-	41	31	-
2	4.94	0.39	25	22	27	59	54	+
3	4.96	0.38	24	23	25	54	40	-
4	4.08	0.40	15	17	17	39	34	-
5	4.12	0.39	21	20	21	-	43	-
6	4.45	0.38	20	20	-	-	58	-
7	4.43	0.41	23	-	27	59	44	-
8	4.61	0.41	25	-	26	58	40	-
9	4.80	0.40	17	-	-	41	31	+
10	5.02	0.41	20	-	-	43	31	+
11	4.42	0.38	40	-	-	107	98	-
aurothioglucose								
1	4.48	0.45	17	20	20	69	75	+
2	4.57	0.40	0	0	0	81	138	-
3	4.43	0.40	0	0	0	51	75	+
4	3.88	0.36	19	15	15	192	244	+
5	4.24	0.40	4	0	0	39	51	-
6	4.63	0.39	2	0	2	63	104	-
7	4.12	0.43	6	5	6	-	106	-
8	4.66	0.42	0	0	0	111	177	-

Various methods of calculation and washing of erythrocytes have been used in recent studies attempting to establish a correlation between the CBG and clinical effects and side-effects of chrysotherapy (7,10). The results were contradictory, probably due to the different methods used. Our study demonstrated no difference between two washing procedures. We found a strong correlation between the three different procedures of calculating the CBG. Unlike Pedersen et al (10), we did not find any difference between CBG expressed in absolute terms and CBG corrected for the erythrocyte count. This may be due to the small variation of the erythrocyte counts and haematocrits in our patients. Pedersen et al (10) presented no data on haematocrit values and erythrocyte counts in their patients, but recommended this correction in order to predict which patients are likely to develop side-effects. In nearly all patients we detected gold in the washing solution (up to 17% of the whole blood gold concentration), whereas Van der Stadt et al (7) reported that gold was not removable from the erythrocytes.

James et al (14) and Graham et al (15) recently pointed out that higher CBG values found in smokers compared to non-smokers, treated with aurothiomalate. Although the number of patients is small, our findings at least do not exclude that some influence of the smoking habits on the CBG might exist in the aurothioglucose treated patients.

There was a slight but significant increase in CBG in the auranofin-treated patients when the blood was stored at room temperature for one day. In the individual patients the increase was always smaller than the coefficient of variation for that concentration.

Our conclusion is that the contradictory findings in the literature concerning the value of CBG cannot be explained by different washing procedures or different methods of calculating CBG. One possibility remains that the smoking habits of the patients in the different studies, are responsible for the

contradictory findings. This study demonstrates that information on CBG can be obtained without washing the erythrocytes; the indirect method of calculating CBG is sufficient.

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CHAPTER 9

DISCUSSION AND CONCLUSIONS

DISCUSSION AND CONCLUSIONS

As a consequence of the wide clinical spectrum of rheumatoid arthritis (RA) on the one hand, and the absence of a specific laboratory test as a quantitative parameter on the other, the effect of treatment in rheumatological practice is usually judged by general assessment. The decision as to whether or not a patient with RA is responding is based on clinical and laboratory information. In order to substantiate this decision the physician considers at the same time partly subjective variables such as morning stiffness, the severity of pain, number of painful and swollen joints, fatigue as well as erythrocyte sedimentation rate and haemoglobin level.

Clinical trial: merits of auranofin? For use in the single blind clinical trial comparing the efficacy and safety of aurothioglucose and auranofin in 52 patients with rheumatoid arthritis (chapter 2) we formalized this general assessment, using multivariate analysis. The index of disease activity (IDA) we used comprises the four following variables: morning stiffness, number of tender joints, haemoglobin level and erythrocyte sedimentation rate; this IDA was adapted from the index described by Mallya et al. By means of the IDA we were able to study the response of each patient and of patient populations as a whole. Many aurothioglucose-treated patients had to be withdrawn due to toxic reactions during the first year of treatment, while on the contrary many auranofin-treated patients were withdrawn after 6 months of treatment due to lack of effect. This prompted us to compare patients in both treatment groups who completed one year of therapy (n = 14) as well as patients who dropped out during the first year of therapy (n = 26). In both comparisons aurothioglucose-treated patients turned out to have improved more. The auranofin-treated patients withdrawn because of lack of efficacy (n = 10) were treated after withdrawal with D-penicillamine; the majority of these responded acceptably well. All in all, auranofin turned out to be less toxic but also less effective than aurothioglucose. In our opinion the therapeutic value of auranofin lies between that of aurothioglucose and that of hydroxy-

chloroquine therapy.

Genetic factors influencing benefit and risk in gold treatment. After the report of Stastny in 1977 that genetic factors play a role in the pathogenesis of rheumatoid arthritis, several studies have demonstrated associations between HLA-antigens and the occurrence of side effects of phase II antirheumatic drugs. However, to our knowledge only one congress presentation is available, which discusses the possible association between HLA-antigens and responsiveness to drug treatment. In agreement with the literature we found (chapter 3) HLA-DR3 more frequently in patients developing serious toxicity during aurothioglucose treatment than in those who did not (35% versus 9%). Due to the low frequency of severe adverse reactions in the auranofin-treated patients, no association with HLA-antigens was found in this treatment group. We demonstrated a statistically significant association between the HLA-DR3-antigen and favourable clinical response to aurothioglucose therapy by measuring the individual degree of response in patients, including those who had to be withdrawn after 4 months of treatment. This association was not found in the auranofin-treated patients, probably because fewer patients showed an excellent response to auranofin and because only 3 auranofin-treated patients happened to be HLA-DR3-positive, versus 6 in the aurothioglucose group. More extensive studies are required in order to establish whether the proneness to develop drug toxicity in the DR3-positive group is associated with excellent responsiveness, i.e. whether or not the good response and the tendency to develop severe toxicity are connected in the same individuals. In order to gain more information on genetic influences it is advisable to consider HLA-typing in controlled clinical studies; it is too early to recommend this method for routine clinical practice.

Immunoglobulin levels: associated with gold-induced toxicity? A patient (chapter 5) who developed selective IgA deficiency during aurothioglucose treatment and at the same time had

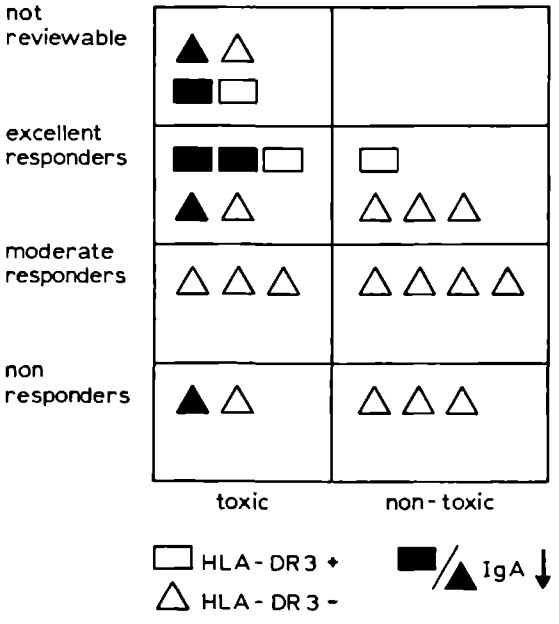

Figure 1. Data about toxicity, degree of response, HLA-DR3 positivity and IgA lowering in 25 aurothioglucose treated patients. Each symbol represents a patient.

generalized dermatitis, made us look for differences in immunoglobulin levels between toxic and non-toxic patients. The group of toxic patients (n = 14) had significantly lower serum IgA and IgG levels than the non-toxic group, both at the start and during treatment (except for IgG at month 12). The serum IgA level seemed to be the most important with regard to toxicity during aurothioglucose treatment: when the immunoglobulin levels were compared at the very moment of toxicity, only the IgA level and not the IgG (or IgM) level was significantly lower in toxic patients than in those not toxic at that moment. Speculations about a possible relation between the serum IgA level and the occurrence of adverse reactions to aurothioglucose are presented (chapter 4). The figure summa-

rizes data on the aurothioglucose-treated patients: toxicity, degree of response, HLA-DR3 positivity and whether or not they developed a subnormal IgA level. It has been thought that patients with an adverse reaction respond better than those without an adverse reaction; from the admittedly small population of patients we studied, it cannot be concluded that toxic patients and non-toxic patients respond differently: no gross differences can be read from this graphic representation of our material. The present data will have to be extended by further studies before definite conclusions can be drawn as to their value in predicting toxicity. Our data suggest, however, that patients with subnormal serum IgA are at particular risk and may be future candidates for dose reduction once IgA becomes subnormal.

Loose stools: a definite, specific auranofin side effect. A change in bowel habits is the most frequent adverse reaction to the orally absorbable gold compound. Many (44%) of the auranofin-treated patients reported the occurrence of loose stools at some time during the study. Arguments for a direct effect of auranofin on ion and water absorption are given in chapter 6. We felt justified to continue auranofin treatment in patients with loose stools, although no data on biopsy material were available. In our opinion postmarketing surveillance of this side effect is necessary.

Monitoring serum gold levels: sense or nonsense? It has been suggested that maintenance of serum gold levels above a certain level (300 μg/100 ml for aurothiomalate) would produce better clinical effects, although others claim the contrary. Using our method of individual scoring of responses, we studied a possible correlation between serum gold levels and the degree of response to aurothioglucose as well as to auranofin (chapter 7). We found no such correlation either in the aurothioglucose- or in the auranofin-treated patients; the excellent responders in the aurothioglucose group had serum gold levels far below 300 μg/100 ml. No differences in serum gold

levels were found between patients with and without loose stools during auranofin treatment. In agreement with the literature we found no differences in serum gold levels between toxic and non-toxic aurothioglucose-treated patients. The serum gold level in most auranofin-treated patients declined in the course of one year of treatment. After one year, a statistically significant difference (mean serum gold level $\pm$ SD at 16 weeks: 67 $\pm$ 30 µg/100 ml versus 44 $\pm$ 16 µg/100 ml at 52 weeks; $p < 0.05$) was found. Since the literature mentions constant whole blood gold levels in the plateau phase of auranofin treatment, we suggest that this is due to a change in the gold distribution in the blood; we did not measure whole blood gold concentrations in all patients. In our opinion serum gold monitoring during aurothioglucose treatment is useless in clinical practice. For research purposes we advise that gold be measured in serum as well as in whole blood during auranofin treatment.

Cell-bound gold: which method of determination? It has been suggested that the amount of erythrocyte-bound gold is correlated with the incidence of toxic reactions; other investigators claim the opposite. Since different procedures of washing erythrocytes and different methods to determine the cell-bound gold concentration had been used, these data were not comparable. We demonstrated (chapter 8) that the different washing methods and the different methods of calculating the amount of erythrocyte-bound gold could not explain the abovementioned conflicting results. Our findings are compatible with the suggestion in the literature that the smoking habits of the patients in the different studies could be responsible for the contradictory findings. It is not necessary to measure CBG: we showed that this can reliably be deduced from measuring the gold concentration in serum and whole blood, respectively.

HOOFDSTUK 10

SAMENVATTING

Dit laatste, Nederlandstalige hoofdstuk is een beknopte weergave, in eenvoudige termen, van hoofdstuk 9, waarin de wetenschappelijke samenvatting en enkele slotbeschouwingen staan.

Bij de behandeling van patienten met reumatoide arthritis, waarbij de medikamenteuze therapie overigens één onderdeel is in een geheel van maatregelen, worden vaak goudinjekties gebruikt. Dit gebeurt al meer dan 60 jaar ondanks het vaak voorkomen van bijwerkingen die soms ernstig kunnen zijn. Meerdere studies hebben de werkzaamheid van goud bij reumatoide arthritis duidelijk aangetoond. Het werkingsmechanisme van goud is echter nog steeds onbekend.
Wanneer de diagnose reumatoide arthritis vaststaat wordt met goudinjekties begonnen als er onvoldoende reaktie is op behandeling met lichtere middelen, die worden aangeduid met de naam: niet-steroidale analgetische antiflogistica. Deze naam geeft aan dat:
- het gaat om stoffen die niet verwant zijn aan bijnierschorshormonen (en dus de gevaren van die stoffen ook niet met zich meebrengen)
- het stoffen zijn, die zowel pijnstillend als ontstekingsremmend werken.
Ze worden nogal eens gegeven in combinatie met antimalariamiddelen. Indien er sprake is van een ernstige, snel tot toenemende gewrichtsschade leidende reumatoide arthritis, kan de behandeling met antimalariamiddelen worden overgeslagen en wordt direct begonnen met goudinjekties in combinatie met genoemde niet-steroidale analgetische antiflogistica.

In hoofdstuk 2 wordt verslag gedaan van een onderzoek, waarbij de werkzaamheid en de veiligheid van een nieuw ontwikkeld goudpreparaat in tabletvorm (auranofin) vergeleken werden met die van het reeds tientallen jaren gangbare goudpreparaat (aurothioglucose). Dit laatste preparaat kon alleen maar via injektie worden toegediend. De "goudtabletten" bleken minder vaak

ernstige bijwerkingen te veroorzaken dan het injecteerbare goudpreparaat, echter de werkzaamheid was eveneens geringer.

In hoofdstuk 3 wordt de invloed beschreven, die erfelijkheidsfactoren kunnen hebben op de uitwerking van de geneesmiddel therapie van reumatoide arthritis. Gebleken is, dat zowel het krijgen van bijwerkingen, als de mate van gunstig reageren op goudinjekties, deels door erfelijke factoren van de patient worden bepaald. De uitkomsten van ons onderzoek, dat een vrij beperkte omvang had, mogen zeker nog niet veralgemeend worden tot een omschreven advies. Indien echter uit verdere studies over grotere aantallen patienten zou blijken dat succes-kans en kans op bijwerkingen door één en dezelfde erfelijkheidsfactor bepaald worden, is het misschien verstandig deze patienten voortaan al bij voorbaat met een lagere dosis goud te behandelen. Het is namelijk komen vast te staan, dat ongewenste nevenwerkingen van goud minstens voor een deel dosis-afhankelijk zijn: verlaging van de dosis kan de bijwerking doen afnemen of verdwijnen, met behoud van een redelijk therapeutisch resultaat.

In hoofdstuk 4 worden argumenten gegeven voor een mogelijke belangrijke rol van het gehalte in serum van een groep van antistoffen (immunoglobuline A, IgA) voor het krijgen van een bijwerking van aurothioglucose. In hoofdstuk 5 wordt een patiente beschreven, die een selectief IgA tekort ontwikkelde tijdens behandeling met aurothioglucose; dit ziektegeval was aanleiding voor de bestudering van het beloop van de IgA gehaltes in het bloed, waarvan hoofdstuk 4 verslag doet. De uitkomsten daarvan zijn, naar onze mening, dusdanig van belang, dat het IgA gehalte voortaan tijdens alle goudbehandelingen in onze kliniek wordt gemeten; patienten met een laag IgA gehalte bij het begin van de goudbehandeling, en degenen bij wie het gehalte snel en/of aanzienlijk daalt, lopen naar onze mening meer kans op een ernstige huidovergevoeligheid. Gaat het ziektebeloop bij die patienten de gunstige kant op, dan wordt de gouddosis verlaagd.

Brijige ontlasting is de meest voorkomende bijwerking van auranofin. De klinische kenmerken van deze nevenwerking, als ook argumenten voor een bepaalde verklaring ervan, worden beschreven in hoofdstuk 6. Wij vinden het aan te raden, dat nâ het op de markt komen van auranofin stelselmatig bij alle of zeer veel gebruikers wordt bijgehouden, hoe de functies van het ingewandstelsel tijdens en ook lang na behandeling met auranofin is. Zo'n registratie en bewerking van de verkregen gegevens, wordt wel aangeduid met de naam "post-marketing surveillance" van een nieuw geneesmiddel.

Er is wel betoogd, dat de goudconcentraties in het serum van patienten van belang zijn om de therapie voor het individuele geval op maat bij te sturen; andere auteurs betwijfelen deze relatie. Onze uitkomsten van onderzoek weergegeven in hoofdstuk 7 lieten géén verband zien tussen de serum goudspiegels en het krijgen van een bijwerking van een van beide goudpreparaten, noch bleek er een correlatie te bestaan met de mate van reageren op de ingestelde therapie. De meting van goudconcentraties in het serum tijdens therapie, als routine, wordt daarom door ons niet aangeraden. Een bijzondere bevinding was dat de serum goudspiegels van de met auranofin behandelde patienten op de lange duur bleken te dalen, ondanks constante dosering. Deze daling was "statistisch significant" na één jaar behandeling. Hoe dit moet worden verklaard is niet zeker; misschien is de verdeling van goud over de bloedbestanddelen anders in het bloed van patienten bij wie de therapie gunstig verloopt (meer goud aan bloedcellen, minder in serum).

In hoofdstuk 8 worden verschillende methodes vergeleken om de hoeveelheid goud gebonden aan de rode bloedlichaampjes te meten. Er bleek een goede correlatie te bestaan tussen de verschillende methoden. De conclusie was: de hoeveelheid cel-gebonden goud kan betrouwbaar berekend worden uit de serumconcentratie en de concentratie in het volledige bloed; het bewerkelijke meten van de goudconcentratie aan/in de bloedcellen apart is dus niet nodig. In onze beperkte gegevens vonden wij

géén opvallende relatie tussen het hebben van een ernstige nevenwerking van aurothioglucose en de mate van goudbinding aan rode bloedcellen.

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 10 juli 1953 te Goirle geboren. In 1971 behaalde hij het diploma HBS-B aan de Rijks HBS te Helmond. Daarna studeerde hij aan de Katholieke Universiteit van Nijmegen en slaagde in december 1978 voor het artsexamen. In januari 1979 begon hij zijn opleiding tot internist in de Kliniek voor Inwendige Ziekten (hoofd: Prof.Dr. C.L.H. Majoor) van het St. Radboudziekenhuis te Nijmegen. Van januari 1981 tot eind december 1982 was hij werkzaam binnen de afdeling Reumatologie (hoofd: Prof.Dr. L.B.A. van de Putte) en binnen de vakgroep Farmacologie (voorzitter Prof.Dr. C.A.M. van Ginneken; werkgroep Farmacokinetiek en Klinische Farmacologie, Prof.Dr. F.W.J. Gribnau) in welke periode het onderzoek werd verricht, waarvan dit proefschrift het verslag is. Sinds januari 1983 is hij weer werkzaam als arts-assistent binnen de kliniek voor Inwendige Ziekten (hoofd: Prof.Dr. A. van 't Laar).

Stellingen
behorende bij het proefschrift van
P.L.C.M. VAN RIEL

I

Het gunstig reageren op aurothioglucose-injecties, bij patiënten met een reumatoïde arthritis, wordt deels door erfelijke factoren bepaald.

Dit proefschrift

II

Reumatoïde arthritis patiënten met een van meet af aan, of later tot stand gekomen, verlaagd serum IgA-gehalte hebben een grotere kans op het krijgen van een bijwerking van de aurothioglucose-behandeling dan patiënten met een verhoogd serum IgA-gehalte.

Dit proefschrift

III

De meest voorkomende bijwerking van auranofin, brijige ontlasting, is het gevolg van een direct toxisch effect van het orale goudpreparaat op de darmmucosa.

Dit proefschrift

IV

Het meten van serum- of plasmagoudconcentraties tijdens behandeling met parenteraal toegediende goudpreparaten heeft géén therapeutische consequentie.

Dit proefschrift

V

Een ernstige bijwerking van de aurothioglucose-behandeling gaat niet altijd gepaard met een gunstige therapeutische reactie.

Dit proefschrift

VI

Hoewel het spreekwoord 'De ochtenstond heeft goud in de mond' letterlijk op de helft van de bestudeerde patiënten van toepassing was, gold de uitspraak 'Eind goed al goed' toch meer voor de andere helft van de groep patiënten.

Dit proefschrift

VII

Het belang van een optimale farmacotherapie van de nederlandse reumapatient is gediend met een goed functionerend 'Centrum voor klinisch-farmacologisch onderzoek van antireumatica'

VIII

Het beoordelen van de kwaliteit van een hoogleraar op basis van citatie-analyse via de naam van de eerste schrijver is onjuist, die hoogleraren die hun promovendi het eerste auteursschap gunnen worden hierdoor sterk benadeeld

IX

Het benoxaprofen 'schandaal' mag reden zijn te stellen dat farmacokinetisch onderzoek voor registratie óók, zo men wil juist, bij de groep van oudere patienten en bejaarden verricht dient te worden

X

Dat een nieuwe behandeling iemand zal schaden staat vast, pas na een gedegen gecontroleerde studie wordt het duidelijk of er ook voldoende iemanden genoeg baat bij hebben

XI

De tijd lijkt rijp om nieuwe geneesmiddelen alleen via het 'monitored release'-systeem toe te laten voor registratie

XII

Het is van belang bij een patient met een erosieve, seronegatieve, niet purulente, oligo- of polyarthritis te blijven zoeken naar een oorzakelijk agens

Steere A C , Grodzicki R L , Kornblatt A N et al , *The spirochetal etiology of lyme disease* N Engl J Med 308 733 1983

Grahame R , Armstrong R , Simmons N et al , *Chronic arthritis associated with the presence of intrasynovial rubella virus* Ann Rheum Dis 42 2, 1983

XIII

Een gouden toekomst mag slechts dan aan de croissanteneen hier te lande beloofd worden, indien de nederlander van overheidswege gedwongen wordt zijn vakantie binnen de eigen landsgrenzen door te brengen

Nijmegen, 27 mei 1983

P L C M van Riel